HPJ HEALTHY POPULATIONS JOURNAL

Research Protocol

The Impact of Exercise on Cardiotoxicity in Pediatric Cancer Survivors: A Scoping Review Protocol

Stephanie J. Kendall [1,2], BSc.; Jodi E. Langley [2,3], MSc.; Bruce N. Crooks [2,4], MD; Nicholas Giacomantonio [5,6], MD; Stefan Heinze-Milne [2,3], PhD; Will J. Johnston [1,2], MSc; Melanie R. Keats [1,2], PhD; Sharon L. Mulvagh [5,6], MD; & Scott A. Grandy [1,2], PhD

[1] School of Health and Human Performance, Dalhousie University
[2] Beatrice Hunter Cancer Research Institute, Halifax, Nova Scotia, Canada
[3] Faculty of Health, Dalhousie University
[4] Department of Pediatrics, IWK Health Centre, Halifax, Nova Scotia, Canada
[5] Department of Medicine, Dalhousie University
[6] Nova Scotia Health Authority, Halifax, Nova Scotia, Canada

DOI: https://doi.org/10.15273/hpj.v2i2.11294

Abstract

Introduction: Childhood and adolescent cancer survivors treated with anthracyclines and chest-directed radiation therapy have a much higher risk of developing cardiovascular complications into adulthood. Exercise is one intervention that may mitigate some of these adverse treatment-related effects. Nevertheless, efforts to consolidate this evidence are limited, and a review is required to summarize the impact of current exercise interventions on managing cardiac-related side effects of cancer treatments in pediatric cancer survivors. ***Objective:*** This scoping review protocol describes the methods used to explore the current literature characterizing exercise interventions and their reported cardiac-related outcomes for managing cardiotoxicity in childhood and adolescent cancer survivors. ***Methods:*** Joanna Briggs Institute guidelines for conducting and reporting scoping reviews will be followed. Studies considered for this review must include an exercise intervention with cardiac surveillance conducted at two or more time points. Intervention participants must have received a cancer diagnosis ≤19 years of age and received anthracyclines or chest-directed radiation therapy. ***Conclusion/Discussion:*** This scoping review protocol provides extensive details regarding the methods used, will enhance the transparency of reporting, and will improve the quality of the final scoping review manuscript. Outputs from the completed scoping review manuscript will summarize the breadth of literature reporting on exercise interventions used to manage treatment-related cardiotoxicity in childhood and adolescent cancer survivors.

Introduction

A significant long-term health issue for childhood and adolescent cancer survivors (CACS) is a heightened cardiovascular disease risk due to cancer therapy (Bansal et al., 2014; Hausner et al., 2008). CACS who receive cardiotoxic cancer therapies, such as anthracyclines and chest-directed radiation therapy, experience a greater risk of heart dysfunction and cardiovascular disease (CVD) later in life (Armenian et al., 2018; Chow et al., 2019; Hausner et al., 2008; Lipshultz et al., 2013; McGowan et al., 2017). Specifically, the long-term impact of cardiotoxic treatments on the heart includes decreased left ventricular (LV) mass, wall thickness, contractility, and fractional shortening (Scott et al., 2011). When CACS are compared with their healthy siblings, above-normal LV afterload has been reported in the CACS (Lipshultz et al., 2012). Together, these effects place CACS at twice the risk for developing CVD than their siblings (Chao et al., 2016). Additionally, CACS with CVD have an 11-fold increase in overall mortality risk, making CVD the leading cause of non-malignant death in this population (Armenian et al., 2018; Chao et al., 2016). Effective non-cardiotoxic treatments and interventions are needed to decrease the impact of cardiotoxic agents on heart health among CACS.

Few strategies are available to mitigate cardiotoxicity in CACS. For example, administering less cardiotoxic treatments (e.g., synthetic analogues of natural compounds vs. organic versions such as doxorubicin) is an option, but these treatments are not always used in CACS (Sun et al., 2014; Xu et al., 2015). As another example, dexrazoxane administered concurrently with anthracycline treatments has cardioprotective effects in CACS (Asselin et al., 2016; Kopp et al., 2019; Reichardt et al., 2018). However, this pharmaceutical approach is associated with additional adverse effects, such as decreased fertility and possibly an increased risk of developing secondary malignant neoplasms (Eneh & Lekkala, 2022).

In light of the tremendous CVD burden among CACS and limited pharmaceutical strategies to reduce risk, current guidelines suggest screening for CVD (Armenian et al., 2015; Lipshultz et al., 2012; Mulrooney et al., 2009; Tukenova et al., 2010). CVD risk screening commonly includes cardiac imaging, such as two-dimensional echocardiography, and may include cardiopulmonary exercise testing or serum cardiac biomarker analysis (Armenian et al., 2015; Wolf et al., 2020). Unfortunately, many CACS are not closely monitored after being transferred to adult care, despite these recommendations. Complementary interventions may be one way to improve cardiotoxicity management in CACS.

Using exercise therapy as a means of managing cardiotoxicity is emerging as a promising strategy that is supported by preclinical research. Indeed, studies using animal models treated with cardiotoxic agents suggest that exercise reduces cardiotoxicity by minimizing cardiovascular risk factors through improving cardiovascular fitness, preserving cardiac structure and function, minimizing inflammation and preventing oxidative stress of heart tissue (Avila et al., 2019; Chao et al., 2016; Chicco et al., 2005; Greene & Hennessy, 2015; Guo & Wong, 2014; Hayward et al., 2012; Hofmann & Franz, 2013; Hydock et al., 2008; Jones et al., 2013). Notably, both light and voluntary exercise have been demonstrated to mitigate cardiotoxicity pre-, during, and post-treatment in animal models (Hydock et al., 2012). This preclinical research justifies subsequent clinical research studies.

While limited, early clinical research in CACS indicates that exercise may be essential in preventing and managing cardiotoxicity. Jones et al. (2014) found that high activity levels are associated with fewer adverse cardiovascular outcomes in a dose-response. Specifically, ≥9 metabolic equivalents of task hours per week of physical activity was associated with a 7%

absolute risk reduction in poor cardiovascular outcomes in adult survivors of childhood Hodgkin lymphoma (Jones et al., 2014). More recently, Morales et al. (2020) demonstrated that CACS maintained a healthy LV ejection fraction during a supervised in-hospital exercise intervention, while the standard care group did not show the same effects. These findings are consistent with the available data suggesting the cardioprotective impact of exercise in the general population and the growing evidence base among adult cancer survivors showing a decreased risk of adverse cardiac effects among those who partake in exercise interventions (Keats et al., 2016; Kirkham et al., 2017; Manson et al., 2002; Tian & Meng, 2019). Notably, no corollary evidence exists that exercise in CACS is unsafe or increases cardiovascular risk (Wurz, McLaughlin, Lategan, Chamorro Viña, et al., 2021; Wurz, McLaughlin, Lategan, Ellis, & Culos-Reed, 2021).

Exercise interventions for CACS can be characterized by the FITT (frequency, intensity, time, and type) principle. The FITT principle can be used to prescribe the exercise dose (Billinger et al., 2015). The frequency is the number of sessions per week, the intensity is how hard the individual should exercise, time is the number of minutes per session, and type is the exercise modality (e.g., walking, resistance training).

Based on a preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* (Peters et al., 2020), no systematic or scoping reviews have been published, and no reviews are currently underway exploring exercise interventions to manage cardiotoxicity among CACS. A scoping review on the topic could provide important information about the breadth of evidence available, offer guidance for future exercise interventions designed to prevent cardiotoxicity in CACS, and identify where more research is necessary. While several reviews are available, none have explored the impact of exercise interventions on heart health in CACS (Huang & Ness, 2011; Upshaw, 2020; Varghese et al., 2021; Wogksch et al., 2021; Wurz, McLaughlin, Lategan, Ellis, & Culos-Reed, 2021).

This scoping review aims to fill a significant gap in knowledge by summarizing the breadth of exercise-based interventions targeting cardiac health in CACS and charting the outcomes of the interventions on cardiac health. This protocol paper, in turn, seeks to detail the scoping review methodologies to improve the transparency and quality of the final review manuscript.

Research Question

1. What is the breadth of exercise interventions available to manage cardiotoxicity in CACS?
    a. How are the exercise interventions described regarding the FITT (Frequency, Intensity, Time, and Type) principle?
2. How does the current literature describe the outcomes of exercise interventions on cardiac health among CACS?

Inclusion and Exclusion Criteria

Participants

This review includes studies involving CACS diagnosed at 19 years of age or younger, as defined by the Canadian Cancer Society, who have received treatments warranting cardiac surveillance (Canadian Cancer Statistics Advisory Committee et al., 2021). These treatments include anthracycline administration, chest-directed radiation, or a combination of anthracycline treatment and chest-directed radiation (Armenian et al., 2015). CACS may be currently receiving treatment or have received treatment in the past.

Concept

The core concept of this scoping review is to summarize the content, nature, and outcomes of any exercise interventions that target individuals who survived childhood or adolescent cancer, intending to decrease treatment-induced CVD during childhood and into adulthood. Exercise interventions of all durations will be included in the review and must include at least a baseline (pre-) and post-intervention measurement of cardiac health. Exercise interventions with measurements conducted at more than two-time points will also be included.

Context

This review will consider exercise interventions performed in any setting, including, but not limited to, a participant's home (i.e., self-directed or online), community facilities, and hospitals. Additionally, studies must include a measure of cardiac surveillance at two different time points. Cardiac surveillance may include but is not limited to two-dimensional echocardiography, multigated acquisition, or cardiac magnetic resonance (Awadalla et al., 2018).

Exclusion Criteria

Studies without an exercise intervention (e.g., physical activity recall studies, reviews).

Types of Sources

This scoping review will consider experimental and quasi-experimental study designs, including randomized controlled trials, non-randomized controlled trials, pre-post studies, and interrupted time-series studies. Researchers will review the reference lists of relevant systematic and scoping reviews to look for primary studies. Finally, researchers will consider conference papers with sufficient data to extract. If data is insufficient, researchers will attempt to contact the conference paper authors.

Methods

The proposed scoping review will be conducted following the Joanna Briggs Institute (JBI) methodology for scoping reviews (Peters et al., 2020). There are no patient participants and no public involvement in this research's design, conduct, reporting, or dissemination plans. The search for this review was conducted on October 12, 2021.

Search Strategy

Researchers followed JBI's three-step search strategy, including a trial of the search strategy in MEDLINE and Cumulative Index to Nursing and Allied Health Literature (CINAHL), identifying keywords and examining included studies' reference lists (Peters et al., 2020). A health librarian reviewed the keywords (Appendix A) alongside the researchers using the Peer Review of Electronic Search Strategies (PRESS) guidelines (McGowan et al., 2016). Next, the keywords were used to search for other published and unpublished studies.

Information Sources

Researchers searched the following databases: MEDLINE, CINAHL, Embase, Scopus, SPORTDiscus, and PsycInfo, using the finalized search strategy. Additionally, the researchers searched sources of unpublished studies and grey literature, including ProQuest Dissertations and Theses Global and the first 10 pages of Google Scholar. Finally, researchers searched for grey literature (Appendix B) using the Canadian Agency for Drugs and Technologies in Health grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* (Canadian Agency for Drugs and Technologies in Health, 2019). Relevant organizational, governmental, and health care association websites were reviewed, including the Children's Oncology Group, PanCare, Canadian Cancer Society, American Cancer Society, National Cancer Institute, Cancer Research UK, and National Health Institute. Researchers also screened the reference lists of all included sources of evidence for additional studies. Only studies published in English were included, as this is the language of the study team. The reviewers contacted the corresponding authors when there was insufficient information in the articles.

Study/Source of Evidence Selection

Following the search, researchers will collate all identified citations and upload the citations into Covidence (https://www.covidence.org/), removing the duplicates. Covidence is a systematic review software commonly used to conduct and organize reviews. Two independent reviewers will screen titles and abstracts for assessment against the inclusion criteria. Reviewers will retrieve potentially relevant sources and import their citation details into Covidence. Next, two independent reviewers will assess the full text of selected citations in detail against the inclusion criteria. Reviewers will record and report the reasons for excluding sources of evidence during the full-text screening that do not meet the inclusion criteria. If any conflicts arise, reviewers will meet and discuss whether the citation meets the inclusion criteria. The full report will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) flow diagram (Tricco et al., 2018) and the PRISMA 2020 guidelines (Page et al., 2021).

Data Extraction

Two independent reviewers will extract data from papers included in the scoping review using a data extraction tool developed by the reviewers (Appendix C). These data will include specific details about the author(s), year of publication, study aim/purpose, study population, concept, context, study methods, outcomes, and key findings relevant to the review questions. Before data extraction begins, a minimum of two independent reviewers will pilot the data extraction tool for five articles and discuss any additional information that needs to be extracted.

The draft data extraction tool will be modified and revised as necessary while extracting data from each included evidence source. The scoping review will detail any modifications made to the tools after pilot testing. Reviewers will meet to resolve any conflicts.

Data Analysis and Preparation

Researchers will follow the PRISMA-ScR reporting guideline for this scoping review (Tricco et al., 2018). The researchers will present the data in a tabular form that aligns with the study's objective. A narrative summary will accompany these presentations and describe how the findings relate to the review's objectives. Researchers will classify results under specific conceptual categories: study characteristics (including country of origin, study population, study setting, and design); outcomes measures; available interventions (FITT); reported key findings; and implications.

Conclusion

Researchers will conduct the review described in this protocol paper to map the current literature regarding exercise interventions for CACS. This review protocol is essential to enhance the transparency of the scoping review and improve reporting. The resultant full scoping review will identify the breadth of exercise interventions, including the FITT, and the impact of the intervention on the heart health of CACS to guide future research efforts and make recommendations. The search strategy followed the JBI guidelines, and the resultant full scoping review will use the PRISMA-ScR reporting guidelines. The researchers hope that the results of this review will advance the study as a strategy to mitigate cardiac damage among CACS.

Acknowledgements

Shelley McKibbon from Dalhousie University's W.K. Kellogg Health Sciences Library provided extensive knowledge and generous assistance with the search protocol.

Funding

This paper was not funded. However, the following authors are students supported in their programs via the stated funders. Stephanie Kendall is a trainee in the Cancer Research Training Program of the Beatrice Hunter Cancer Research Institute, with funds provided by Saunders Matthey. Jodi Langley is a trainee in the Cancer Research Training Program of the Beatrice Hunter Cancer Research Institute, with funding provided by the Canadian Cancer Society's Carol Ann Cole Graduate Studentship. Will Johnston is a trainee in the Cancer Research Training Program of the Beatrice Hunter Cancer Research Institute, with funds provided by CIBC.

Conflict of Interest

There are no conflicts of interest in this project.

References

Armenian, S. H., Armstrong, G. T., Aune, G., Chow, E. J., Ehrhardt, M. J., Ky, B., Moslehi, J., Mulrooney, D. A., Nathan, P. C., Ryan, T. D., van der Pal, H. J., van Dalen, E. C., & Kremer, L. C. M. (2018). Cardiovascular disease in survivors of childhood cancer: Insights into epidemiology, pathophysiology, and prevention. *Journal of Clinical Oncology, 36*(21), 2135–2144. https://doi.org/10.1200/jco.2017.76.3920

Armenian, S. H., Hudson, M. M., Mulder, R. L., Chen, M. H., Constine, L. S., Dwyer, M., Nathan, P. C., Tissing, W. J. E., Shankar, S., Sieswerda, E., Skinner, R., Steinberger, J., van Dalen, E. C., van der Pal, H., Wallace, W. H., Levitt, G., & Kremer, L. C. M. (2015). Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *The Lancet: Oncology, 16*(3), e123–e136. https://doi.org/10.1016/s1470-2045(14)70409-7

Asselin, B. L., Devidas, M., Chen, L., Franco, V. I., Pullen, J., Borowitz, M. J., Hutchison, R. E., Ravindranath, Y., Armenian, S. H., Camitta, B. M., & Lipshultz, S. E. (2016). Cardioprotection and safety of dexrazoxane in patients treated for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma: A report of the children's oncology group randomized trial Pediatric Oncology Group 9404. *Journal of Clinical Oncology, 34*(8), 854–862. https://doi.org/10.1200/jco.2015.60.8851

Avila, M. S., Siqueira, S. R. R., Ferreira, S. M. A., & Bocchi, E. A. (2019). Prevention and treatment of chemotherapy-induced cardiotoxicity. *Methodist DeBakey Cardiovascular Journal, 15*(4), 267–273. https://doi.org/10.14797/mdcj-15-4-267

Awadalla, M., Hassan, M. Z. O., Alvi, R. M., & Neilan, T. G. (2018). Advanced imaging modalities to detect cardiotoxicity. *Current Problems in Cancer, 42*(4), 386–396. https://doi.org/10.1016/j.currproblcancer.2018.05.005

Bansal, N., Franco, V. I., & Lipshultz, S. E. (2014). Anthracycline cardiotoxicity in survivors of childhood cancer: Clinical course, protection, and treatment. *Progress in Pediatric Cardiology, 36*(1–2), 11–18. https://doi.org/10.1016/j.ppedcard.2014.09.012

Billinger, S. A., Boyne, P., Coughenour, E., Dunning, K., & Mattlage, A. (2015). Does aerobic exercise and the FITT principle fit into stroke recovery? *Current Neurology and Neuroscience Reports, 15*(2), Article 519. https://doi.org/10.1007/s11910-014-0519-8

Canadian Agency for Drugs and Technologies in Health. (2019, April). *Grey matters: A* *practical tool for searching health-related grey literature.* https://www.cadth.ca/sites/default/files/is/Grey%20Matters_EN-2019.doc

Canadian Cancer Statistics Advisory Committee, Canadian Cancer Society, Statistics Canada, & Public Health Agency of Canada. (2021, November). *Canadian cancer statistics 2021*. Canadian Cancer Society. https://cancer.ca/Canadian-Cancer-Statistics-2021-EN

Chao, C., Xu, L., Bhatia, S., Cooper, R., Brar, S., Wong, F. L., & Armenian, S. H. (2016). Cardiovascular disease risk profiles in survivors of adolescent and young adult (AYA) cancer: The Kaiser Permanente AYA cancer survivors study. *Journal of Clinical Oncology, 34*(14), 1626–1633. https://doi.org/10.1200/jco.2015.65.5845

Chicco, A. J., Schneider, C. M., & Hayward, R. (2005). Voluntary exercise protects against acute doxorubicin cardiotoxicity in the isolated perfused rat heart. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology, 289*(2), R424–R431. https://doi.org/10.1152/ajpregu.00636.2004

Chow, E. J., Leger, K. J., Bhatt, N. S., Mulrooney, D. A., Ross, C. J., Aggarwal, S., Bansal, N., Ehrhardt, M. J., Armenian, S. H., Scott, J. M., & Hong, B. (2019). Paediatric cardio-oncology: Epidemiology, screening, prevention, and treatment. *Cardiovascular Research, 115*(5), 922–934. https://doi.org/10.1093/cvr/cvz031

Eneh, C., & Lekkala, M. R. (2022). Dexrazoxane. In *StatPearls*. StatPearls Publishing. Retrieved February 2, 2022, from http://www.ncbi.nlm.nih.gov/books/NBK560559/

Greene, J., & Hennessy, B. (2015). The role of anthracyclines in the treatment of early breast cancer. *Journal of Oncology Pharmacy Practice, 21*(3), 201–212. https://doi.org/10.1177/1078155214531513

Guo, S., & Wong, S. (2014). Cardiovascular toxicities from systemic breast cancer therapy. *Frontiers in Oncology, 4*, Article 346. https://doi.org/10.3389/fonc.2014.00346

Hausner, E., Fiszman, M. L., Hanig, J., Harlow, P., Zornberg, G., & Sobel, S. (2008). Long-term consequences of drugs on the paediatric cardiovascular system. *Drug Safety, 31*(12), 1083–1096. https://doi.org/10.2165/0002018-200831120-00005

Hayward, R., Lien, C.-Y., Jensen, B.T., Hydock, D. S., & Schneider, C. M. (2012). Exercise training mitigates anthracycline-induced chronic cardiotoxicity in a juvenile rat model. *Pediatric Blood & Cancer, 59*(1), 149–154. https://doi.org/10.1002/pbc.23392

Hofmann, U., & Frantz, S. (2013). How can we cure a heart “in flame”? A translational view on inflammation in heart failure. *Basic Research in Cardiology, 108*(4), Article 356. https://doi.org/10.1007/s00395-013-0356-y

Huang, T.-T., & Ness, K. K. (2011). Exercise interventions in children with cancer: A review. *International Journal of Pediatrics, 2011*, Article 461512. https://doi.org/10.1155/2011/461512

Hydock, D. S., Lien, C.-Y., Jensen, B. T., Parry, T. L., Schneider, C. M., & Hayward, R. (2012). Rehabilitative exercise in a rat model of doxorubicin cardiotoxicity. *Experimental Biology and Medicine, 237*(12), 1483–1492. https://doi.org/10.1258/ebm.2012.012137

Hydock, D. S., Lien, C.-Y., Schneider, C. M., & Hayward, R. (2008). Exercise preconditioning protects against doxorubicin-induced cardiac dysfunction. *Medicine and Science in Sports and Exercise, 40*(5), 808–817. https://doi.org/10.1249/mss.0b013e318163744a

Jones, L. W., Fels, D. R., West, M., Allen, J. D., Broadwater, G., Barry, W. T., Wilke, L. G., Masko, E., Douglas, P. S. Dash, R. C., Povsic, T. J., Peppercorn, J. Marcom, P. K., Blackwell, K. L., Kimmick, G., Turkington, T. G., & Dewhirst, M. W. (2013). Modulation of circulating angiogenic factors and tumor biology by aerobic training in breast cancer patients receiving neoadjuvant chemotherapy. *Cancer Prevention Research, 6*(9), 925–937. https://doi.org/10.1158/1940-6207.capr-12-0416

Jones, L. W., Liu, Q., Armstrong, G. T., Ness, K. K., Yasui, Y., Devine, K., Tonorezos, E., Soares-Miranda, L., Sklar, C. A., Douglas, P. S., Robison, L. L., & Oeffinger, K. C. (2014). Exercise and risk of major cardiovascular events in adult survivors of childhood Hodgkin lymphoma: A report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 32*(32), 3643–3650.

Keats, M. R., Grandy, S. A., Giacomantonio, N., MacDonald, D., Rajda, M., & Younis, T. (2016). EXercise to prevent AnthrCycline-based Cardio-Toxicity (EXACT) in individuals with breast or hematological cancers: A feasibility study protocol. *Pilot and Feasibility Studies, 2,* Article 44. https://doi.org/10.1186/s40814-016-0084-9

Kirkham, A. A., Shave, R. E., Bland, K. A., Bovard, J. M., Eves, N. D., Gelmon, K. A., McKenzie, D. C., Virani, S. A., Stöhr, E. J., Warburton, D. E. R., & Campbell, K. L. (2017). Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: A proof-of-concept RCT. *International Journal of Cardiology, 245,* 263–270. https://doi.org/10.1016/j.ijcard.2017.07.037

Kopp, L. M., Womer, R. B., Schwartz, C. L., Ebb, D. H., Franco, V. I., Hall, D., Barkauskas, D. A., Krailo, M. D., Grier, H. E., Meyers, P. A., Wexler, L. H., Marina, N. M., Janeway, K. A., Gorlick, R., Bernstein, M. L., Lipshultz, S. E., & Children's Oncology Group. (2019). Effects of dexrazoxane on doxorubicin-related cardiotoxicity and second malignant neoplasms in children with osteosarcoma: A report from the Children's Oncology Group. *Cardio-Oncology, 5*, Article 15. https://doi.org/10.1186/s40959-019-0050-9

Lipshultz, S. E., Adams, M. J., Colan, S. D., Constine, L. S., Herman, E. H., Hsu, D. T., Hudson, M. M., Kremer, L. C., Landy, D. C., Miller, T. L., Oeffinger, K. C., Rosenthal, D. N., Sable, C. A., Sallan, S. E., Singh, G. K., Steinberger, J., Cochran, T. R., Wilkinson, J. D., American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young … Council on Nutrition, Physical Activity and Metabolism. (2013). Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: Pathophysiology, course, monitoring, management, prevention, and research directions: A scientific statement from the American Heart Association. *Circulation, 128*(17), 1927–1995. https://doi.org/10.1161/cir.0b013e3182a88099

Lipshultz, S. E., Landy, D. C., Lopez-Mitnik, G., Lipsitz, S. R., Hinkle, A. S., Constine, L. S., French, C. A., Rovitelli, A. M., Proukou, C., Adams, M. J., & Miller, T. L. (2012). Cardiovascular status of childhood cancer survivors exposed and unexposed to cardiotoxic therapy. *Journal of Clinical Oncology, 30*(10), 1050–1057. https://doi.org/10.1200/jco.2010.33.7907

Manson, J. E., Greenland, P., LaCroix, A. Z., Stefanick, M. L., Mouton, C. P., Oberman, A., Perri, M. G., Sheps, D. S., Pettinger, M. B., & Siscovick, D. S. (2002). Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *The New England Journal of Medicine, 347*(10), 716–725. https://doi.org/10.1056/nejmoa021067

McGowan, J., Sampson, M., Salzwedel, D. M., Cogo, E., Foerster, V., & Lefebvre, C. (2016). PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *Journal of Clinical Epidemiology, 75,* 40–46. https://doi.org/10.1016/j.jclinepi.2016.01.021

McGowan, J. V., Chung, R., Maulik, A., Piotrowska, I., Walker, J. M., & Yellon, D. M. (2017). Anthracycline chemotherapy and cardiotoxicity. *Cardiovascular Drugs and Therapy, 31*(1), 63–75. https://doi.org/10.1007/s10557-016-6711-0

Morales, J. S., Valenzuela, P. L., Herrera-Olivares, A. M., Baño-Rodrigo, A., Castillo-García, A., Rincón-Castanedo, C., Martín-Ruiz, A., San-Juan, A. F., Fiuza-Luces, C., & Lucia, A. (2020). Exercise interventions and cardiovascular health in childhood cancer: A meta-analysis. *International Journal of Sports Medicine, 41*(3), 141–153. https://doi.org/10.1055/a-1073-8104

Mulrooney, D. A., Yeazel, M. W., Kawashima, T., Mertens, A. C., Mitby, P., Stovall, M., Donaldson, S. S., Green, D. M., Sklar, C. A., Robison, L. L., & Leisenring, W. M. (2009). Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: Retrospective analysis of the Childhood Cancer Survivor Study Cohort. *BMJ, 339*, Article b4606. https://doi.org/10.1136/bmj.b4606

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*(8286), Article n71. https://doi.org/10.1136/bmj.n71

Peters, M. D. J., Marnie, C., Tricco, A. C., Pollock, D., Munn, Z., Alexander, L., McInerney, P., Godfrey, C. M., & Khalil, H. (2020). Updated methodological guidance for the conduct of scoping reviews. *JBI Evidence Synthesis, 18*(10), 2119–2126. https://doi.org/10.11124/jbies-20-00167

Reichardt, P., Tabone, M.-D., Mora, J., Morland, B., & Jones, R. L. (2018). Risk–benefit of dexrazoxane for preventing anthracycline-related cardiotoxicity: Re-evaluating the European labeling. *Future Oncology, 14*(25), 2663–2676. http://dx.doi.org/10.2217/fon-2018-0210

Scott, J. M., Khakoo, A., Mackey, J. R., Haykowsky, M. J., Douglas, P. S., & Jones, L.W. (2011). Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: Current evidence and underlying mechanisms. *Circulation, 124*(5), 642–650. https://doi.org/10.1161/CIRCULATIONAHA.111.021774

Sun, J., Zhang, J., Yan, W., Chen, C., Wu, G., Abbasi, S., Pham, B., Lee, S., Cheng, J., Memon, N. B., & Xi, Y. (2014). Iloprost prevents doxorubicin mediated human cardiac progenitor cell depletion. *International Journal of Cardiology, 176*(2), 536–539. https://doi.org/10.1016/j.ijcard.2014.07.031

Tian, D., & Meng, J. (2019). Exercise for prevention and relief of cardiovascular disease: Prognoses, mechanisms, and approaches. *Oxidative Medicine and Cellular Longevity, 2019*, Article 3756750. https://doi.org/10.1155/2019/3756750

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA extension for Scoping Reviews (PRISMA-ScR): Checklist and explanation. *Annals of Internal Medicine, 169*(7), 467–473. https://doi.org/10.7326/M18-0850

Tukenova, M., Guibout, C., Oberlin, O., Doyon, F., Mousannif, A., Haddy, N., Guérin, S., Pacquement, H., Aouba, A., Hawkins, M., Winter, D., Bourhis, J., Lefkopoulos, D., Diallo, I., & de Vathaire, F. (2010). Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *Journal of Clinical Oncology, 28*(8), 1308–1315. https://doi.org/10.1200/jco.2008.20.2267

Upshaw, J. N. (2020). Cardioprotective strategies to prevent cancer treatment-related cardiovascular toxicity: A review. *Current Oncology Reports, 22*(7), Article 72. https://doi.org/10.1007/s11912-020-00923-w

Varghese, S. S., Johnston, W. J., Eekhoudt, C. R., Keats, M. R., Jassal, D. S., & Grandy, S. A. (2021). Exercise to reduce anthracycline-mediated cardiovascular complications in breast cancer survivors. *Current Oncology, 28*(5), 4139–4156. https://doi.org/10.3390/curroncol28050351

Wogksch, M. D., Goodenough, C. G., Finch, E. R., Partin, R. E., & Ness, K. K. (2021). Physical activity and fitness in childhood cancer survivors: A scoping review. *Aging and Cancer, 2*(4), 112–128. https://doi.org/10.1002/aac2.12042

Wolf, C. M., Reiner, B., Kühn, A., Hager, A., Müller, J., Meierhofer, C., Oberhoffer, R., Ewert, P., Schmid, I., & Weil, J. (2020). Subclinical cardiac dysfunction in childhood cancer survivors on 10-years follow-up correlates with cumulative anthracycline dose and is best detected by cardiopulmonary exercise testing, circulating serum biomarker, speckle tracking echocardiography, and tissue doppler imaging. *Frontiers in Pediatrics, 8*, Article 123. https://doi.org/10.3389/fped.2020.00123

Wurz, A., McLaughlin, E., Lategan, C., Chamorro Viña, C., Grimshaw, S. L., Hamari, L., Götte, M., Kesting, S., Rossi, F., van der Torre, P., Guilcher, G. M. T., McIntyre, K., & Culos-Reed, S. N. (2021). The international Pediatric Oncology Exercise Guidelines (iPOEG). *Translational Behavioral Medicine, 11*(10), 1915–1922. https://doi.org/10.1093/tbm/ibab028

Wurz, A., McLaughlin, E., Lategan, C., Ellis, K., & Culos-Reed, S. N. (2021). Synthesizing the literature on physical activity among children and adolescents affected by cancer: Evidence for the international Pediatric Oncology Exercise Guidelines (iPOEG). *Translational Behavioral Medicine, 11*(3), 699–708. https://doi.org/10.1093/tbm/ibaa136

Xu, Z., Zhu, L., Liu, X., Gong, X., Gattrell, W., & Liu, J. (2015). Iloprost for children with pulmonary hypertension after surgery to correct congenital heart disease. *Pediatric Pulmonology, 50*(6), 588–595. https://doi.org/10.1002/ppul.23032

Appendix A

Search Strategy

1	(Cancer* OR Neoplas* OR Leukemia* OR Leukaemia* OR Tumor* OR Tumour* OR Lymphoma* OR Chemotherap* OR Malignanc* OR Anthracycline* OR "Antineoplastic Agent*" OR Immunotherap* OR "Monoclonal Antibod*" OR "Tyrosine Kinase Inhibitor*" OR Radiation OR Radiology)
2	Child* OR Adolescent* OR Teen* OR "Young Adult*" OR "Early Child*" OR Pediatric* OR Paediatric* OR Infant* OR Toddler* OR Bab* OR Juvenile* OR "Pre Pubescent*"
3 cancer and child	1 AND 2
4	Exercise* OR "Resistance Training*" OR Aerobic* OR "Motor Activity" OR "Exercise Therap*" OR "Physical Activit*" OR Training OR "Physical Fitness" OR Exertion OR Yoga OR Pilates OR "Dance Therap*" OR "Tai Ji" OR Qigong
5	Exp Exercise/
6 exercise	4 OR 5
7 cancer and child and exercise	3 AND 6
8	Myocarditis* OR "Heart Failure" OR Cardiotoxic* OR Cardiomyopath* OR Heart* OR "Radiation Injury*"
9 Cancer and child and exercise and heart	7 AND 8

Appendix B

Grey Literature Check

Google
Cancer AND Child AND Exercise AND Cardio*
Cancer AND Pediatric AND Exercise AND Cardio*
Cancer AND Child AND "Physical Activity" AND Cardio*

ProQuest
cancer AND child AND exercise AND cardiotoxicity
cancer AND pediatric AND exercise AND cardiotoxicity
cancer AND child AND "Physical Activity" AND cardiotoxicity

Websites
Canadian Cancer Society, American Cancer Society, Cancer Research UK, National Health Institute, American College of Sports Medicine, Canadian Society for Exercise Physiologists, and Canadian Cardiology Society

Appendix C

Data Extraction Template

Study ID	
Title	
Author	
Year	
Country	
Aim	
Inclusion criteria	
Exclusion criteria	
Method of recruitment	
Cancer type	
Cancer treatment	
Time since diagnosis	
Number of participants	
Age	
FITT of exercise intervention	
Duration of exercise intervention	
Setting of exercise intervention	
Instructor of exercise intervention	
Outcome measures	
Key results	
Implications	
Limitations	