Heart failure in childhood cancer survivors – A systematic review protocol

Tove Berg (tove.berg@vgregion.se)
University of Gothenburg Institute of Clinical Sciences: Goteborgs universitet Institutionen for kliniska vetenskaper https://orcid.org/0000-0003-1725-2549

Jens Böhmer
University of Gothenburg Institute of Clinical Sciences: Goteborgs universitet Institutionen for kliniska vetenskaper

Bright Nwaru
Göteborgs universitet Institutionen för medicin: Goteborgs universitet Institutionen for medicin

Kristjan Karason
Göteborgs universitet Institutionen för medicin: Goteborgs universitet Institutionen for medicin

Marianne Jarfelt
University of Gothenburg Institute of Clinical Sciences: Goteborgs universitet Institutionen for kliniska vetenskaper

---

Protocol

Keywords: Childhood Cancer, Anthracyclines, Survivors, Cardiomyopathy, Heart failure Protocol and guidelines, Meta-analysis, Protocol and guidelines, Systematic review

Posted Date: July 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-628315/v1

Version of Record: A version of this preprint was published at Systematic Reviews on March 29th, 2022.
See the published version at https://doi.org/10.1186/s13643-022-01929-0.

Abstract

Background

Over the past decades, survival rate for childhood cancer has greatly improved. However, the risk of late cardiac complications after such treatment remains high. Previous studies have shown that the risk for heart failure among childhood cancer survivors is significantly higher than that observed in the general population. The aim of this systematic review is to identify, critically appraise and synthesize existing population-based studies reporting on the frequency of heart failure, both incidence or prevalence, that may develop after treatment of childhood cancer.

Method:

The following databases will be searched from their inception date until May 17th 2021: Medline, Embase, Scopus, CINAHL, CAB International, AMED, Global Health, Psycinfo, Web of science and Google Scholar. Population-based studies reporting on the incidence and/or prevalence of heart failure after treatment of any type of childhood cancer will be included. Screening of articles, data extraction and quality assessment will be performed independently by two reviewers. The quality and risk of bias in the studies included will be assessed by using the Effective Public Health Practice Project tool. A narrative synthesis of the extracted data will be undertaken and, for studies that are sufficiently homogenous, a meta-analysis using random-effects models performed.

Discussion

This systematic review will provide a clearer picture of the epidemiology of heart failure after treatment of childhood cancer. Collected data will be of value for future childhood cancer treatment protocols and also offer guidance for post-treatment cardiac surveillance among survivors.

Systematic review registration

This protocol follows the structure of the recommendation of the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) and has been submitted in PROSPERO on April 28th 2021, awaiting assignment of registration number.

Background

The survival rate for childhood cancer has greatly improved over the past decades and is today above 80%. As a result, the cohort of adult childhood cancer survivors is steadily growing (1–3). Correspondingly, the risk of long term-side effects of cancer treatment including debilitating and sometimes fatal conditions is high, with a cumulative incidence of about 40 % after 30 years of follow-up (4). The most common forms of late complications and causes of death among childhood cancer survivors include secondary malignancies, cardiovascular diseases and pulmonary disorders (5, 6). Reports from the US Childhood Cancer Survivor Study has reported up to seven times higher risk of

premature death due to cardiac complications among childhood cancer survivors as compared to the general population (5, 6). A wide variation of heart diseases in childhood cancer survivors have been reported (7–10). The most common cardiac condition in this population is heart failure, which has earlier been reported in a wide range with up to 15-fold higher risk compared to young people from the general population (4, 7, 11, 12).

According to the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) guidelines for the management of heart failure (HF) from 2013, HF is largely a clinical diagnosis based on a careful history and physical examination and cannot be characterized by a single diagnostic test. The cardinal clinical manifestations of HF are dyspnea, fatigue and fluid retention (13). The severity of HF was initially defined by the New York Heart Association (NYHA) functional classification, in which patients are assigned to one of four groups based on how much they are limited during physical activity (Table 1) (14). In addition, ACCF/AHA have developed a classification including four stages that complements the NYHA system (Table 2) (13). Both classifications provide useful information about the presence and severity of HF and have valuable prognostic implications. ACCF and AHA have defined HF as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood (13). Accordingly, the European Society of Cardiology (ESC) state HF as a clinical syndrome, characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by clinical signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality (15)

Table 1
NYHA functional classification

Classification	Definition
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
NYHA, New York Heart Association; HF, heart failure.	

Table 2
ACCF/AHA stages of heart failure.

Stage	Definition
A	At high risk for HF but without structural heart disease or symptoms of HF.
B	Structural heart disease but without signs or symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.
D	Refractory HF requiring specialized interventions.

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure.

Previous echocardiography investigations in childhood cancer survivors, who did not experience any symptoms, have reported a variety of structural and/or functional cardiac abnormalities, referred to as subclinical cardiotoxicity. Still, the observed frequency of such echocardiographic aberrations is highly inconsistent, and ranges from 0 % to 57% (16). There is no general consensus on how to define or classify subclinical cardiotoxicity (16, 17), which may, in part, explain the differences between previous studies. Furthermore, it is unclear to what degree subclinical cardiotoxicity in childhood cancer survivors may evolve into overt heart failure over time (16, 18).

Treatment with anthracyclines (ACs) has greatly improved survival rates in in children with cancer (19). A drawback is that the ACs are cardiotoxic and the risk for developing heart failure increases in parallel with the cumulative dose of these chemotherapeutics (8, 16, 20, 21). A dose of anthracyclines below 250 mg/m^2 has been report to be associated with at low risk for cardiotoxicity, but for susceptible persons no dose is safe and individual risk factors including demographic features and comorbidities need to be considered as well (11, 21–23). The relative risk for heart failure due to different types of anthracyclines is arbitrary and mainly based on the assumption that hematological toxicity and cardiotoxicity are correlated (24). Published data on what doses of different ACs are safe with respect to cardiotoxicity and risk for subsequent heart failure are contradictory (25). Other types of chemotherapeutic drugs that have been seen to contribute to the cardiotoxic effect of ACs include tyrosine kinase inhibitors, alkylating agents and cisplatin (9). Radiation of the chest is also a risk factor for heart failure after treatment of childhood cancer and may also contribute to coronary artery disease and valvular heart disease (8, 26, 27). The highest risk for heart failure development is seen in survivors that have been treated with both anthracyclines and radiotherapy (8).

Patients treated for childhood cancers during the 1990s have shown a lower incidence of late cardiac complications, as compared to previous eras, particularly for coronary artery disease. This is probably due to modifications of treatment protocols, which include reductions in cardiotoxic chemotherapeutics and less cardiac radiation (10, 28). A report from the Dutch Childhood Oncology Group–Long-Term Effects After Childhood Cancer (DCOG-LATER) study 2019 showed decreased mortality due to heart failure when recent treatment periods were compared with older ones, but, somewhat paradoxically, an increase in the incidence of heart failure in more modern eras (26).

A synthesis of population-based studies reporting on the frequency of heart failure after childhood cancer treatment and examining whether the incidence and prevalence of this condition is changing over time is important. Not least, since the acquisition of such epidemiological knowledge is likely to be of value when generating future treatment protocols for childhood cancer and organizing post-treatment cardiac surveillance programs.

Objectives

The primary aim of this systematic review is to identify, critically appraise and synthesize existing population-based studies reporting on the incidence and/or prevalence of heart failure in persons who have survived a minimum of 5-years after treatment of childhood cancer. Heart failure incidence and prevalence will be compared for different time-eras including the 1970s, 1980s, 1990s, 2000s, and 2010s. A secondary aim is to identify and study the impact of different risk factors on the development of heart failure after childhood cancer treatment including type and dose of cancer therapy, and also examine the potential impact of demographic factors and comorbidities. Below follows the PICO (participants, interventions, comparators, and outcomes) framework we used to formulate the research questions. There are no specific group of comparison.

- Participants: 5-years survivors of childhood cancer.
- Interventions: Childhood cancer treatment.
- Comparators: No comparison group.
- Outcomes: Heart failure incidence and/or prevalence. Risk factors for development of heart failure.

Primary question

What is the incidence and/or prevalence of heart failure in 5-year survivors of childhood cancer post treatment?

Secondary question

Can we identify any individual and/or treatment related risk factors for development of heart failure in this patient group?

Methods

This systematic review protocol follows the structure of the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)(29). The protocol has been submitted to International prospective register of systematic reviews PROSPERO on April 28th 2021 and awaiting assignment of registration number. The reporting of this systematic review will be in accordance with the guidelines for Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and in compliance with the guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analysis

(PRISMA) (30, 31). Any amendments to the protocol and rationale during the systematic review will be accounted for in the final report.

Ethical considerations

The present study will be based solely on previously reported data and does not involve any contact with patients. Hence, there are no concerns that require ethical vetting.

Eligibility criteria

This systematic review will include population-based studies that report on the incidence and/or prevalence of heart failure after treatment of all types of childhood cancer. Randomized controlled trials will not be included, since clinical studies of this kind are not expected to address our research question. The subjects of interest are patients who have received cancer treatment before the age of 18 years and have survived for a minimum of 5 years. Patients with all cancer types who have received all forms of cancer treatments will be included. Animal studies will be excluded from the literature search.

Study identification / Information sources

The following databases will be searched from their inception date until May 17th 2021: Medline, Embase, Scopus, CINAHL, CAB International, AMED, Global health, Psycinfo, Web of science and Google Scholar. Grey literature will also be screened to identify studies not published in mainstream journals. Reference lists of retrieved papers will be screened to identify possible additional articles of relevance. There will be no language restrictions and efforts will be made to translate studies reported in languages other than English.

Search strategy

Our Medline search strategy is given in Additional file 1 and this will be adapted in searching the other databases.

Study selection

Retrieved papers will be exported to Endnote for further screening. The titles and abstracts of all articles retrieved from database searches will be screened independently by two reviewers according to the eligibility criteria. After the screening is finished the reviewers will compare their results and a third reviewer will arbitrate in case of any disagreements that cannot be solved by a discussion between the two reviewers. Papers potentially eligible at this stage will be transferred to the next step, which will involve full text screening, again performed independently by two reviewers with a third reviewer arbitrating any disagreement. The screening process will be reported in a PRISMA flow diagram and include the total number of abstracts assessed, as well as the complete number of all full texts retrieved.

Data extraction and management

A standardized data extraction form will be developed for the study to retrieve data and applied independently by two reviewers (TB and JB). The extracted information will be based on the PICO structure and include:

- Participant characteristics: e.g. sources of subject, inclusion criteria, characteristics of cohort group (age, gender, geographical region, socio-economic status, ethnicity, co-morbidities, ICD cancer diagnosis).

- Exposure to childhood cancer treatment: e.g. anthracyclines, tyrosine kinase inhibitors, alkylating agents and cisplatin, radiation to chest.

- Primary outcomes: e.g. ICD Heart failure diagnosis, year of diagnosis, age at diagnosis, incidence or prevalence of heart failure in the cohort, frequency of heart failure-related death.

- Secondary outcomes: identification of risk factors for development of heart failure in the population.

General information (e.g. reviewer, date of data extraction, record number, author, article title), study characteristics (e.g. study design, study aim), methods of follow up, missing data, analysis and quality assessment will also be collected. The ability of this process to capture intended data will be piloted with a couple of the studies before a complete data-extraction from all included studies is carried out.

When data extraction is completed the reviewers will compare their results and a third reviewer (MJ) will arbitrate in case there are any disagreements. If relevant information is missing in a significant article an effort will be made to contact the authors of the paper so lacking data may be retrieved.

Quality assessment

The quality and risk of bias in all included studies will be assessed by using The Effective Public Health Practice Project tool (EPHPP) (32). The EPHPP tool enables detailed assessment of strengths and weaknesses of individual studies as it provides individual ratings for six domains of study quality assessment. For each study, the risk of bias will be categorized as low, moderate or high. Two independent reviewers will perform the quality appraisal and a third reviewer will arbitrate in case of any disagreement.

Analysis/ data synthesis

Descriptive data and characteristics for all included studies will be presented in tables. We will undertake a narrative synthesis of the extracted data and describe the key characteristics and findings of each study. We will search, compare, and contrast concepts and findings across studies in order to determine the prevailing concept of the underlying evidence. A meta-analysis using random-effects models will be performed for studies that are sufficiently homogenous with respect to their methods, population, design, intervention/exposure, outcomes and assessment. We will use the I-squared statistic, which provides an indication of study heterogeneity in the effect estimates between studies that is due to chance. Furthermore, we will perform subgroup analysis after splitting the study population into groups of age, country of residence, comorbidities and sex as well as e.g. time-eras, cancer treatment types and years

from diagnosis. If a sufficient number of studies can be retrieved, we will perform a meta-regression to explore the potential reasons for the heterogeneity in estimates between studies. We will also undertake sensitivity analysis to explore any potential scenario that can change the conclusion of our findings, e.g. by excluding all low-quality studies from the meta-analysis and evaluate whether the results from high-quality studies differ from all studies included together. Finally, we will assess a potential publication bias using funnel plots and by applying the Begg and Egger test (33, 34). The meta-analysis will be undertaken in Stata version 15. All variables will be expressed with a 95 % confidence interval (CI).

Discussion

Heart failure is a late complication after treatment of childhood cancer, which is both common, serious and sometimes fatal. Still, there are many uncertainties surrounding the epidemiology of this condition. The frequency of heart failure in different subgroups of childhood cancer survivors varies greatly. Although the risk for heart failure development increases along with the dose of ACs, some patients develop impaired cardiac function even after low doses. This underlines the fact that features other than the cumulative AC dos are of importance. For example, patients treated with both anthracyclines and chest radiation display the highest risk.

In the present review, we will only focus on population-based studies. Thus, we will avoid bias caused by wide variations in heart failure frequency due to differences specific subpopulations. To our knowledge there are no previous systematic reviews on heart failure after childhood cancer treatment grounded on population-based studies. We intend to provide a clearer picture of the epidemiology of heart failure after all childhood cancer treatment. Data on the type and dose of cancer treatment will be collected in order to study the impact of these factors on heart failure development. In addition, we will gather information on demographic features and comorbidities to study to what degree such characteristics may constitute risk factors.

Despite improved survival after treatment of childhood cancer, the incidence of late cardiac complications remains high, not least heart failure. Therefore, it is of great importance to systematically collect data from available studies to generate knowledge about the long-term cardiotoxicity of chemotherapy and radiation applied when treating childhood cancer. This systematic review will provide information of value for future treatment protocols for children with cancer and will also offer guidance for post-treatment cardiac surveillance. Early detection of cardiac abnormalities may allow for early intervention, which is likely to improve the outcome in this patient population.

List Of Abbrevations

ACCF: American College of Cardiology Foundation

AHA: American Heart Association

HF: heart failure

NYHA: New York Heart Association

ESC: European Society of Cardiology

ACs: anthracyclines

PROSPERO: International prospective register of systematic reviews

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis

MOOSE: Meta-Analysis of Observational Studies in Epidemiology

EPPH: The Effective Public Health Practice Project tool

PICO: Participants, Interventions, Comparators, and Outcomes

Declarations

Funding

The project is supported by The Swedish Childhood Cancer Foundation. The funder has no role in developing the review protocol.

Competing interest

The authors declare no competing interest.

Availability of data and material

Not applicable

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Authors' contributions

This study was conceived by TB, MJ and JB. The protocol has been developed by all authors. TB wrote the first draft of the protocol manuscript and all authors gave input to the final draft. TB and JB will independently perform study screening, data extraction and quality assessment of articles, whereas MJ and KK will arbitrate any disagreements and provide field expertise. BN is an epidemiologist who has substantial experience in undertaking systematic reviews and will provide knowledge of the systematic review structure and statistical analysis expertise. MJ is the guarantor of the review.

Acknowledgements

The project is supported by The Swedish Childhood Cancer Foundation.

References

1. Gatta GBL, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. Lancet Oncol. 2014;15(1):35–47.
2. Gustafsson GHMKP. Childhood cancer incidence and survival in Sweden. 1985–2010. http://www.forskasverige.se/wp-content/uploads/ChildhoodCancerIncidenceandSurvivalinSweden1984_2010.pdf: From the Swedish Childhood Cancer Registry; 2013. Accessed 14 June 2021.
3. Olle Bergman LF, Gabor Hont E, Johansson P, Ljungman E, Munck-Wikland H, Nahi. Jan Zedenius Cancer i siffror 2018, Populärvetenskapliga fakta om cancer. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2018-6-10.pdf: Socialstyrelsen, Cancerfonden; 2018. Accessed 14 June 2021.
4. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355(15):1572–82.
5. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27(14):2328–38.
6. Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, Robison LL, Yasui Y. Cause-Specific Late Mortality Among 5-Year Survivors of Childhood Cancer: The Childhood Cancer Survivor Study. J Natl Cancer Inst. 2008;100:1368. –1379(19 ..
7. Gudmundsdottir T, Winther JF, de Fine Licht S, Bonnesen TG, Asdahl PH, Tryggvadottir L, et al. Cardiovascular disease in Adult Life after Childhood Cancer in Scandinavia: A population-based cohort study of 32,308 one-year survivors. Int J Cancer. 2015;137(5):1176–86.
8. van der Pal HJ, van Dalen EC, van Delden E, van Dijk IW, Kok WE, Geskus RB, et al. High risk of symptomatic cardiac events in childhood cancer survivors. J Clin Oncol. 2012;30(13):1429–37.
9. Lipshultz SE, Adams MJ, Colan SD, Constine LS, Herman EH, Hsu DT, et al. 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. 2013;128(17):1927–95.

10. Fidler MM, Reulen RC, Henson K, Kelly J, Cutter D, Levitt GA, et al. Population-Based Long-Term Cardiac-Specific Mortality Among 34 489 Five-Year Survivors of Childhood Cancer in Great Britain. Circulation. 2017;135(10):951–63.
11. Feijen E, Font-Gonzalez A, Van der Pal HJH, Kok WEM, Geskus RB, Ronckers CM, et al. Risk and Temporal Changes of Heart Failure Among 5-Year Childhood Cancer Survivors: a DCOG-LATER Study. J Am Heart Assoc. 2019;8(1):e009122.
12. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. Bmj. 2009;339:b4606.
13. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147–239.
14. Committee NYHAC. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: ed: Little Brown & Co; 1994.
15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Rev Esp Cardiol (Engl Ed). 2016;69(12):1167.
16. Kremer LC, van der Pal HJ, Offringa M, van Dalen EC, Voute PA. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol. 2002;13(6):819–29.
17. Khouri MG, Douglas PS, Mackey JR, Martin M, Scott JM, Scherrer-Crosbie M, et al. Cancer therapy-induced cardiac toxicity in early breast cancer: addressing the unresolved issues. Circulation. 2012;126(23):2749–63.
18. Lipshultz SE, Karnik R, Sambatakos P, Franco VI, Ross SW, Miller TL. Anthracycline-related cardiotoxicity in childhood cancer survivors. Curr Opin Cardiol. 2014;29(1):103–12.
19. Armenian SH, Hudson MM, Mulder RL, Chen MH, Constine LS, Dwyer M, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2015;16(3):e123-36.
20. Ramos A, Meyer R, Korfhagen J, Wong K, Kaplan S. Echocardiographic evaluation of adriamycin cardiotoxicity in children. Cancer Treat Rep [Internet]. 1976; 60(9):[1281-4 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00308576/full. Accessed 14 June 2021.
21. Volkova M, Russell R 3. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011;7(4):214–20. rd. .

22. Jarfelt M, Kujacic V, Holmgren D, Bjarnason R, Lannering B. Exercise echocardiography reveals subclinical cardiac dysfunction in young adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2007;49(6):835–40.
23. Sadurska E. Current Views on Anthracycline Cardiotoxicity in Childhood Cancer Survivors. Pediatr Cardiol. 2015;36(6):1112–9.
24. van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev. 2010(5):CD005006.
25. Feijen EA, Leisenring WM, Stratton KL, Ness KK, van der Pal HJ, Caron HN, et al. Equivalence Ratio for Daunorubicin to Doxorubicin in Relation to Late Heart Failure in Survivors of Childhood Cancer. J Clin Oncol. 2015;33(32):3774–80.
26. Feijen E, Font-Gonzalez A, Van der Pal HJH, Kok WEM, Geskus RB, Ronckers CM, et al. Risk and Temporal Changes of Heart Failure Among 5-Year Childhood Cancer Survivors: a DCOG-LATER Study. J Am Heart Assoc. 2019;8(1):e009122.
27. Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol. 2010;28(8):1308–15.
28. Mulrooney DA, Hyun G, Ness KK, Ehrhardt MJ, Yasui Y, Duprez D, et al. Major cardiac events for adult survivors of childhood cancer diagnosed between 1970 and 1999: report from the Childhood Cancer Survivor Study cohort. BMJ. 2020;368:l6794.
29. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
30. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000;283(15):2008–12.
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
32. Effective Public Health Practice Project. Quality Assessment Tool for Quantitative Studies. https://merst.ca/wp-content/uploads/2018/02/quality-assessment-tool_2010.pdf. Accessed 14 June 2021.
33. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101.
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629–34.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1MedlineSearchStrategies.pdf
- Additionalfile2PRISMAP.docx
- Additionalfile2PRISMAP.pdf