

Aerobic Exercise for Optimizing Cardiopulmonary Fitness in Childhood Cancer  
Survivors Treated with a Known Cardiotoxic Agent: A Meta-Analysis

by

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Submitted in partial fulfillment of the requirements for  
the degree of Master of Science

at

Dalhousie University  
Halifax, Nova Scotia  
August 2016

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## **Dedication Page**

I would like to dedicate this thesis to my girlfriend, Katie; my parents, Paula and Chris; and all of my siblings, Ben, Emily, Sarah, Thomas, Amanda, Samantha and Abigail. Thank you for your unwavering support and confidence in me.

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## Abstract

Cardiotoxicity (CT) is a side effect of cancer treatment that can damage the heart and increase cardiovascular disease (CVD) risk. Furthermore, CT and reduced physical activity (PA) contribute to a sustained reduction in cardiopulmonary fitness (CPF), an independent predictor of CV mortality. Recent studies have explored the potential of aerobic exercise as a cardioprotective strategy, and many have reported CPF as an outcome. The main purpose of this review was to synthesize evidence from the existing childhood cancer survivor (CCS) studies examining the effect of aerobic exercise on CPF. The specific objectives were to investigate how certain clinical characteristics (e.g., treatment status) and exercise parameters (e.g., program length) change the effect of exercise on CPF. Pooled evidence from the nine included studies suggests that aerobic exercise has a statistically and clinically significant positive effect on CPF. Findings on the moderating effect of clinical characteristics and exercise parameters were insignificant.

## List of Abbreviations Used

AC	Anthracycline
ACSM	American College of Sports Medicine
ALL	Acute lymphoblastic leukemia
CCS	Childhood cancer survivors
CCT	Controlled clinical trial
CHD	Coronary heart disease
CON	Control group, standard of care
CPF	Cardiopulmonary fitness
CREC	Cardiac Review and Evaluation Committee
CSEP	Canadian Society for Exercise Physiology
CT	Cardiotoxicity
CV	Cardiovascular
CVD	Cardiovascular disease
DEX	Dexrazoxane
EX	Exercise group, aerobic
HF	Heart failure
HR <sub>max</sub>	Maximum heart rate
ICTRP	International Clinical Trials Registry Platform
LVEF	Left ventricular ejection fraction
PA	Physical activity
PE	Potentially eligible
POEM	Pediatric Oncology Exercise Manual
RCT	Randomized controlled trial
SD	Standard deviation
SE	Standard error
TCD	Total cumulative dose
VO <sub>2</sub> max	Oxygen consumption at maximal exercise
VO <sub>2</sub> peak	Oxygen consumption at peak exercise
WHO	World Health Organization

## Glossary

<b>Term</b>	<b>Definition</b>
Attrition Bias	Refers to systematic differences between groups in withdrawals from a study; also referred to as ‘incomplete outcome data bias’
Cardioprotection	Any strategy used to mitigate the damage to heart tissue caused by cancer treatment
Cardiotoxicity	The damage to heart tissue caused by certain cancer treatments
Cardiotoxic Risk Factor	A factor that increases the risk of developing CVD after being exposed to a cardiotoxic treatment
Citation	A single search strategy result, before deduplication
Detection Bias	Refers to systematic differences between groups in how outcomes are determined; this form of bias is prevented by successful blinding of outcome assessors
Dose	The combination of frequency, time per session, and intensity of an aerobic exercise program (e.g., hours/week + intensity OR hours/day + intensity)
Duplicate Publication	A publication that reports on data from the same study as another publication, but is not an identical report
Grey Literature	Literature that is not formally published in sources such as books or journal articles (e.g., conference abstracts/proceedings)
Hawthorne Effect	The change in behaviour of participants in a study due to their awareness of being observed
Late Effect	Effect of cancer treatment that may present as early as a few months and as late as several years after initiation of treatment
Long-term Survivor	A cancer survivor that was diagnosed $\geq 5$ years previously
Performance Bias	Refers to systematic differences between intervention and control group due to exposure to factors other than the intended intervention
Publication Bias	Refers to a systematic difference between the studies included in the review, and the studies that are missed; caused by the preferential publication of studies that suggest a beneficial intervention or a larger effect size
Record	A single search strategy result, after deduplication
Relative VO <sub>2</sub> Peak	VO <sub>2</sub> peak relative to a person’s body weight in kg; ml/kg/min
Reporting Bias	Refers to systematic differences between reported and unreported findings/outcome measures across studies; also

referred to as ‘within-study publication bias’ or ‘selective reporting bias’

Selection Bias

Refers to systematic differences between baseline characteristics of the groups that are compared; this form of bias is prevented by successful randomization and allocation concealment

Sensitivity Analysis

A repeat of the primary analysis or meta-analysis, using alternative decisions or ranges of values for decisions that were arbitrary or unclear; answers the question “Are the findings of the primary analysis robust to any arbitrary decisions regarding included studies or data?”

Small-study Effects

A tendency for the effect estimates of smaller studies to differ systematically from those of larger studies; due to publication bias, or other reasons

## Acknowledgements

First and foremost, I would like to thank my co-supervisors, Drs. Melanie Keats and Scott Grandy for the integral roles they have both played since day 1 of my master's degree. If it were not for your guidance, patience, and consistent support and feedback, I would not have made it to this point (at least not with all of the knowledge and skills I now have to show from my degree). I am especially grateful for your understanding and for the important lessons you facilitated through the evolution of my thesis project, both in terms of the research area, as well as the research process. I am also grateful for the additional workload you both accepted in assisting me with screening studies for my systematic review (which was not a light load, to say the least). In summary, you are both awesome. I would also like to take this opportunity to thank my thesis committee members, Drs. Derek Kimmerly and Tony Reiman, for all of their help, and for their unwavering support through my degree (and all of the changes to my thesis project). Your insightful feedback has helped me to think critically about my research and the conclusions I have drawn from it. I would also like to thank Dr. Robin Urquhart, Dr. Jill Hayden, and Ms. Robin Parker for providing me with guidance on the systematic review and meta-analysis process, based on their methodological expertise in this type of research. Special thanks to those who helped me with navigating the statistical methods of my thesis, including Michael and Yunsong from the Atlantic PATH research team, and Yihao from the Dalhousie Statistical Consulting Service. Another special thanks to my external examiner, Dr. Anna Huguet, for generously agreeing to be a part of my thesis defense committee, and for providing valuable recommendations that I have both incorporated into this thesis, and that will help with publication of this research. Last (but not least) I would like to thank all of those who have made up (and who continue to make up) my non-academic support network. This includes my (enormous) family, my friends, both near and far, and my girlfriend (you all know who you are). Whether it was being there to help me de-stress through some of my struggles, lending an ear or an eye when I needed some feedback, or joining me in celebrating my progress and small victories, thank you all for always being there when I needed you. I could not have done it without all of you.

## Chapter 1: Introduction

### I. Cardiotoxicity in Childhood Cancer Survivors

The most drastic increase in survival rate among childhood cancer survivors (CCS) occurred between the early 1960s and the late 1990s, with the 5-year cancer survival rate increasing from 30% to nearly 80%.<sup>1-3</sup> Survival rate has since continued to improve at a slower pace.<sup>1,2,4</sup> It should be noted that recent increases in childhood cancer survival are due largely to advances in cancer diagnosis and treatment, including common treatment such as radiation therapy and combination chemotherapy.<sup>5</sup> Unfortunately, with the increase in survival rate, there has also been an increase in the recognition and concern over certain late effects of these cancer treatments. Of all the late effects of cancer treatment,<sup>6,7</sup> cardiovascular disease (CVD) is one of the most detrimental,<sup>8</sup> and frequently occurring.<sup>9</sup>

A major contributor to the increased risk of CVD in cancer survivors is cardiotoxicity (CT); a side effect of chemotherapy,<sup>10,11</sup> and radiation therapy.<sup>12-14</sup> Importantly, the severity of CT is dependent on a number of different risk factors (i.e., cardiotoxic risk factors).<sup>15-21</sup> One of the most important cardiotoxic risk factors is time since initial exposure.<sup>17-19,22,23</sup> This cardiotoxic risk factor means that those who survive the longest after cancer treatment are at higher risk of developing cardiotoxic effects.<sup>24</sup> Thus, since CCS on average have a higher survival rate than adult cancer survivors (e.g., 78% versus  $\leq 33\%$  for acute lymphoblastic leukemia [ALL];<sup>7</sup> 83-85% versus 63% for all cancers<sup>25</sup>), they are at a proportionally greater risk of developing CT-mediated CVD later in life.<sup>9,26-</sup>

Also, CT may play a larger role in the overall risk of CVD in CCS than it does in any adult cancer survivor subset.<sup>31,32</sup> This may be due to the fact that the age-matched general population experiences a much lower prevalence and incidence of cardiovascular (CV) morbidity or mortality at a younger age.<sup>32</sup> It is supported by the finding that the disparity in the incidence of severe, life-threatening or fatal late effects (including CVD) between CCS and their siblings not only does not resolve with time, it becomes more pronounced, even though the general population has an increasing incidence of similar conditions with advancing age.<sup>8,33</sup> Furthermore, studies have recently shown an increase in the incidence of traditional cardiac risk factors (e.g., obesity, prediabetes, cholesterol levels, physical inactivity),<sup>34,35</sup> and overall CVD risk<sup>34</sup> in Canadian and American children. Increases in some of these risk factors have even been observed specifically for CCS.<sup>36</sup> These risk factors compound the risk of CCS developing CVD.

## II. Cardioprotection in Childhood Cancer Survivors

Many researchers have attempted to determine the optimal way to mitigate CT and reduce the risk of CVD in CCS (otherwise known as ‘cardioprotection’) while maintaining the efficacy of cancer treatment.<sup>37</sup> Currently, the primary cardioprotective strategy is dose restriction, both in terms of reducing the total dose from repeated exposures received over the patient’s total lifetime (i.e., total cumulative dose),<sup>38–41</sup> and reducing maximal drug concentration in the blood (i.e., peak serum dose).<sup>42,43</sup> Unfortunately, while dose restriction is highly effective against CT related to some cancer treatments (e.g., radiation),<sup>44,45</sup> it appears to be far less effective against the CT related to others (e.g., chemotherapy).<sup>41,46,47</sup>

Consequently, researchers have attempted to use other cardioprotective tactics against chemotherapy-related CT.<sup>48-50</sup> Each of these tactics has demonstrated a different degree of efficacy in the CCS population, with the most effective being dexrazoxane (DEX; a pharmacological cardioprotective agent).<sup>37</sup> Unfortunately, the use of DEX in practice is limited to the adult cancer survivor population, specifically breast cancer survivors.<sup>37</sup> Although drugs like DEX show promise for protecting CCS from CT, there is room for improvement still, and the search for other cardioprotective strategies able to supplement the benefits of the existing cardioprotective strategies continues.

### III. A Potential Non-Pharmacological Cardioprotective Strategy

Aerobic exercise already has established benefits against numerous chronic conditions (e.g., CVD,<sup>51-57</sup> diabetes,<sup>58</sup> stroke<sup>59</sup>) in both adults,<sup>60,61</sup> and children.<sup>62</sup> Furthermore, some studies have shown similar CV benefit in CCS.<sup>63,64</sup> Based on these findings, it is possible that aerobic exercise could provide protection against the development of CT-mediated CVD. Given the documented benefits of aerobic exercise for cancer survivors, standard of care for adult cancer survivors has been established,<sup>65-68</sup> and guidelines/recommendations for CCS have been proposed by experts in the field.<sup>69</sup> Thus, it is clear that the CV benefit of aerobic exercise in CCS has been recognized.

A primary goal of the existing aerobic exercise recommendations for CCS is to mitigate the deficit in cardiopulmonary fitness (CPF) experienced by CCS.<sup>70-72</sup> Although not directly indicative of cardioprotection, CPF may be an appropriate surrogate marker for cardioprotection as previous evidence from the general population has shown that reduced CPF is an independent indicator of increased risk of CVD mortality.<sup>73-75</sup> It has also been previously suggested that the reduction in CPF experienced by CCS is at least



partially related to cardiotoxic damage (with less diminished CPF being associated with less cardiotoxic treatment),<sup>70</sup> and that CPF increases in response to aerobic exercise in CCS.<sup>69</sup> This is also supported by the fact that previous research has found that as much as 70-85% of a decrease in CPF can be attributed to reduced cardiac output.<sup>76</sup>

Given that the existing literature on the relationship between aerobic exercise and CPF in CCS is primarily composed of small studies that lack power, and/or have not been assessed for clinical relevance, the quality of the evidence informing these recommendations needs to be improved prior to the establishment of standard of care. Furthermore, there is a lack of specific evidence on the optimal parameters of exercise (i.e., intensity, frequency, duration per session, program length, and activity type) for increasing CPF in CCS with specific clinical characteristics (i.e., treatment status, cancer diagnosis, cancer treatment[s], etc.), even though evidence from past reviews in adult cancer survivors suggests that at least some of these factors may have some moderating effect.<sup>77,78</sup> Therefore, the existing consensus-based aerobic exercise recommendations for CCS may not be optimal for affording cardioprotection to all CCS.

#### IV. Purpose and Objectives

Two recent meta-analyses reported the general effect of aerobic exercise on CPF in adult cancer survivors.<sup>77,78</sup> Unfortunately, neither reported on the effect of aerobic exercise on CPF in CCS. In addition, three past systematic reviews of CCS studies (including one that encompassed all studies with patients treated for hematological cancer) provided some evidence for the effect of aerobic exercise on CPF.<sup>79-81</sup> However, none of these focussed specifically on either the effect of aerobic exercise on CPF, nor this effect within the population of CCS treated with cardiotoxic therapy. Therefore, the

main purpose of the review was to specifically focus on synthesizing evidence from the existing CCS studies that have examined the effect of aerobic exercise on CPF, in survivors that have been treated with a known cardiotoxic agent. This more focussed review has both research and clinical implications beyond previous broader reviews as it provides preliminary evidence to strengthen the link between CT, CPF, and aerobic exercise.

Building on previous reviews conducted in the adult cancer population, the specific objectives of this review were to examine the effect of the following independent variables on CPF: activity type; intervention length; exercise intensity; exercise session frequency; duration per session; reported adherence to exercise interventions; treatment status (i.e., exercise during versus exercise following treatment); time since diagnosis (i.e., early-onset versus late-onset CT); primary cancer diagnosis; cancer treatment(s); and the level of aerobic exercise prescription (i.e., below range, within range, or above range), relative to the current established recommendations for CCS in the Pediatric Oncology Exercise Manual (POEM).<sup>69</sup>

## Chapter 2: Literature Review

In Canada, the 5-year cancer survival rate for children (ages 0-19 years) increased by 11% between 1990 and 2006.<sup>4</sup> The most recent data from the Canadian Cancer Society suggests that children diagnosed with any type of cancer have a 5-year survival rate of 83-85%.<sup>25,82</sup> Unfortunately, with the growing population of CCS, there is also an increased recognition and concern over the ‘late effects’ of cancer treatment in these survivors. Late effects of cancer treatment are those presenting a few months to several years after initiation of treatment. These include, but are not limited to, a reduction in bone density, cognitive deficits, distress, fatigue, infertility, pulmonary dysfunction, sexual dysfunction, and CVD.<sup>6,7</sup> Of all the late effects experienced by CCS, CVD is one of the most common, with one study showing a higher relative risk of congestive heart failure (HF; a type of heart-related CVD) than second malignant neoplasm.<sup>9</sup> CVD in CCS is also one of the most lethal late effects, with one study finding that major cardiac events are the third most common cause of death among CCS after recurrence of primary malignancy, and second malignancy.<sup>8</sup>

### I. Cardiovascular Disease in Childhood Cancer Survivors

In addition to its highly detrimental, and prevalent effect on all cancer survivors, CVD poses a serious threat to survivorship in children.<sup>83,84</sup> In one study of CCS who had been diagnosed with acute lymphoblastic leukemia (ALL), which is the most common cancer diagnosis in children,<sup>7</sup> 57% of the participants had some form of late CV abnormality (i.e., increased afterload or decreased contractility).<sup>22</sup> It has also been reported that HF was one of the most prominent conditions displayed in survivors from the Childhood Cancer Survivor Study.<sup>9,18,30</sup> Other studies have also reported the increased

incidence of other cardiac events in long-term CCS (i.e., time since diagnosis  $\geq 5$  years).<sup>26–</sup>

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Not surprisingly, CVD is the leading non-malignant cause of death in CCS.<sup>30</sup> Furthermore, the incidence of cardiac mortality exceeds the levels observed in age-sex-matched cohorts from the general population.<sup>30,85</sup> For example, in one study, the rate of cardiac mortality in CCS was 7 times that of the general population.<sup>30</sup> One study even found that all CCS, regardless of treatment received, are at an increased age-adjusted 30-year risk of myocardial infarction, stroke, or coronary death, when compared to their siblings.<sup>36</sup> It is believed that the increases in CV risk and mortality experienced by CCS following treatment are compounded by an increase in traditional risk factors for atherosclerotic disease in this population, including elevated non-high-density lipoprotein cholesterol, elevated fasting insulin levels, and decreased physical activity [PA] levels.<sup>36,86,87</sup> Thus, CV health must be considered in the long-term monitoring strategy for CCS.

## II. Cardiotoxicity of Cancer Treatment

CT, which is a major putative mechanism of increased incidence of CVD and cardiac mortality in cancer survivors, is generally accepted to refer to the damage to heart tissue caused by toxins (e.g., cancer treatments). Multiple studies have shown that CT can be caused by a variety of adjuvant therapies.<sup>13,22,24,88–102</sup> However, studies have shown that the strongest association with CT belongs to chemotherapy,<sup>10,11</sup> and/or radiation treatment.<sup>12–14,24,91,102,103</sup> More recently, it has been reported that targeted therapies (e.g., certain alkylating agents, antimetabolites, etc.) are also associated with CT.<sup>10,103,104</sup> Together, this evidence suggests that the higher relative risk of cardiac damage and

dysfunction in CCS when compared to the age-matched healthy population is related to many of the treatments CCS receive.

Out of all of the treatment regimens associated with CT, the combination of anthracycline therapy (AC; a class of chemotherapy) and irradiation of the left chest, typically results in the most severe cardiotoxic effects.<sup>13,14,24,91,102</sup> Each of these is also individually associated with quite severe cardiotoxic effects. In many cases, this is due either to their more frequent use,<sup>105</sup> or the irreversible damage they are more likely to cause.<sup>12</sup> The risk of developing CVD due to AC or chest radiation therapy is dependent on a number of risk factors (i.e., cardiotoxic risk factors). These cardiotoxic risk factors include the total cumulative dose (TCD),<sup>15,16</sup> age at time of exposure,<sup>15,17,18</sup> biological sex,<sup>15,18,19</sup> pre-existing cardiac disease,<sup>15,17,18,20</sup> and traditional CVD risk factors (e.g., obesity, diabetes mellitus, hypertension, physical inactivity, etc.).<sup>15,19–21</sup> Prior exposure to other forms of cardiotoxic therapy (e.g., AC, radiation, alkylating agents, antimetabolites, etc.) can also increase the risk of CVD associated with AC or chest radiation.

The final cardiotoxic risk factor is time since initial exposure.<sup>17–19,22,23,106</sup> This is an important risk factor since it means a low TCD may still result in CVD, it will just take longer. For instance, one study showed that a similar incidence of cardiac abnormality (i.e., reduced fractional shortening) was recorded at less than 10 years follow-up for those who had received more than 500 mg/m<sup>2</sup> (a unit of dosage for chemotherapy) of AC, and at over 10 years follow-up for those who had received less than 500 mg/m<sup>2</sup>.<sup>100</sup> In other words, the longer a person survives following treatment (AC especially) the greater the likelihood that cardiac effects will be observed, regardless of TCD. One study identified

that the increased risk of CV mortality in CCS became significant at 5-10 years following diagnosis, and did not appear to plateau even after 30 years of follow-up.<sup>24</sup>

Time since exposure may be especially important to consider for CCS since the survival potential among children is higher compared to adults. For example, the 5-year relative survival rate for ALL is much higher when diagnosed in childhood than when it is diagnosed in adulthood (ages  $\geq 20$  years).<sup>7</sup> Despite this being favourable for children initially, this higher survival potential may eventually lead to a higher likelihood of developing CT-related CVD. Furthermore, although childhood cancer diagnoses represent less than 1% of all new cancer diagnoses,<sup>7</sup> children may be a special cause for concern when it comes to late-onset CT, since the prevalence of heart disease in the age-matched general population is much lower for children than adults.<sup>31,32</sup> Therefore, the impact of any cardiotoxic treatment on CVD risk will most likely be more significant for younger cancer survivors, who likely otherwise would have been at lower risk than an adult cancer patient.

That being said, recent studies have shown that traditional cardiac risk factors are on the rise in adolescents (12-19 years).<sup>34,35</sup> These include the incidence of obesity,<sup>34</sup> high cholesterol levels ( $\geq 5.2$ mmol/L),<sup>34</sup> and prediabetes.<sup>35</sup> These increases are similar to what has been observed in the adult general population since the 1980s.<sup>107,108</sup> As a result, the number of Canadian adolescents at risk of CVD has increased.<sup>34</sup> Therefore, these increases in both individual risk factors (which are also cardiotoxic risk factors) and overall CVD risk are particularly detrimental to CCS since they compound the risk of developing CVD after exposure to cardiotoxic treatments.

### III. Classifications of Cardiotoxicity

Studies have shown that CT associated with AC and radiation can lead to a variety of CVDs. Specifically, chest radiotherapy significantly increased the risk of myocardial infarction, angina pectoris, HF, and valvular disorders (between 2- and 7-fold),<sup>13</sup> and AC-induced CT is predominantly associated with the increased incidence of HF.<sup>93,101,109–112</sup> While the development of other types of CVD following AC treatment is possible, their incidence is much rarer in comparison to HF.<sup>12</sup> To this effect, the Cardiac Review and Evaluation Committee (CREC) formulated a definition of chemotherapy-associated cardiac dysfunction that includes mainly HF symptoms, among some other criteria.<sup>113</sup> This definition is used to identify and monitor CT following AC therapy.<sup>113</sup>

The majority of studies of the effects of CT are concerned with the incidence of symptomatic outcomes (e.g., myocardial infarction, HF, etc.).<sup>114</sup> Symptomatic outcomes caused by chemotherapy treatments vary by treatment, but share an underlying mechanism, which is generally detectable as a functional change, not a structural one (i.e., LV dysfunction).<sup>115</sup> Conversely, the underlying mechanism of radiotherapy-related CT can generally be detected as a structural change (i.e., fibrosis; the scarring that results from injury to cardiac structures), and has been shown to manifest in different ways for different structures of the heart.<sup>15,116</sup>

In addition to the studies that have detected symptomatic outcomes, other studies have reported effects of both AC,<sup>117,118</sup> and radiation CT<sup>119</sup> that do not meet the threshold of symptomatic damage proposed by the CREC. The most common “asymptomatic” changes caused by CT include subclinical changes in left ventricular ejection fraction (LVEF; a functional cardiac measure classically used to diagnose HF)<sup>118</sup>; and changes in

molecular markers of CT such as cardiac troponins,<sup>120,121</sup> and certain natriuretic proteins.<sup>117</sup> Importantly, these changes will often precede or predict the traditional symptomatic changes in cardiac structure or function. Therefore, it is possible that there is a period prior to symptomatic CT presentation when protective measures can be initiated in order to possibly mitigate the risk of future symptomatic CT.

Researchers also often divide CT symptoms by how long after initial exposure to cardiotoxic treatment they present. The severity of AC-induced CT has often been linked to the timing of symptom presentation, with more severe CT occurring later after initial treatment exposure.<sup>105</sup> Meanwhile, the different timings of radiation-induced CT presentation, and the corresponding severity of cardiotoxic effects, are generally described more vaguely.<sup>15</sup> The lack of distinct correlation between timing of presentation and change in severity of cardiotoxic effect for radiation-induced CT may be due to the longer average delay between treatment initiation and symptomatic CT,<sup>21</sup> and/or the larger proportion of patients that present with changes to cardiac measures that are not symptomatic, and never progress to symptomatic CT.<sup>15</sup> Nonetheless, the emergence of late-onset CT in cancer survivors, as opposed to early-onset CT, may be especially injurious, at least when it is associated with AC.

The underlying reason that treatment-induced cardiac damage remains below the symptomatic threshold initially, is that symptomatic changes in functional measures (i.e., LVEF and fractional shortening<sup>122</sup>) only occur once morphological damage is critical, which takes time. However, once damage is critical, and compensatory mechanisms such as cardiomyocyte hypertrophy,<sup>19,123</sup> contractile reserve,<sup>124,125</sup> and increased adrenergic sympathetic and renin-angiotensin system activity,<sup>126</sup> are no longer effective, functional



deterioration proceeds rapidly,<sup>124,127</sup> and is consequently easily detectable by functional measures. Furthermore, the latent inhibition of cardiac progenitor cell proliferation by cancer treatment impedes the heart's final defense against functional deterioration.<sup>128</sup> Therefore, it is important that cancer patients and health care professionals alike are aware of the seriousness of late-onset symptomatic treatment-induced CT, and both take prophylactic measures against it during the period prior to symptomatic development.

#### IV. Cardioprotection

Since cancer treatment was first associated with late-onset CT,<sup>94</sup> many researchers have attempted to determine the most effective method to protect the heart against it. These methods that have been developed are generally referred to as cardioprotection, and individually as cardioprotective strategies. The effectiveness of a cardioprotective strategy can be determined by weighing its benefit, in terms of minimizing or eliminating the damage caused by CT, against its potential interference with the treatment's intended anticancer effect. For most treatments, the initial cardioprotective strategy has been dose restriction, such as restricting TCD,<sup>38-41</sup> and/or restricting peak serum dose (i.e., for AC, a lower peak serum dose is achieved with continuous rather than bolus infusion),<sup>42</sup> which is related to the dose-dependent nature of CT.<sup>38-41</sup>

For radiation therapy, dose restriction has been shown to have both cardioprotective benefit, and is also able to mostly retain the anticancer efficacy of radiation, making it a favorable tactic against radiation-induced CT, when combined with superficial cardioprotective measures (i.e., field size reduction and cardiac shielding).<sup>44,45</sup>

Unfortunately, dose restriction is a less effective cardioprotective strategy for chemotherapy. One reason for this may be that chemotherapy treatment cannot combine dose reduction with other superficial cardioprotective measures the way radiotherapy can, since it is systemic. Furthermore, while it is generally recommended that TCD of AC should be restricted to 300 mg/m<sup>2</sup>, as risk of cardiotoxic damage increases substantially beyond this TCD (i.e., high-risk of CT),<sup>129,130</sup> the occurrence of CT has also been detected at TCDs as low as 45 mg/m<sup>2</sup> in some cancer survivors,<sup>18</sup> since there is a marked inter-individual variability in susceptibility to CT.<sup>39,40,53-55</sup> This suggests that no TCD is uniformly safe for all cancer patients. Consequently, while dose restriction has shown benefit in mitigating cardiotoxic effects, it is not able to effectively prevent all damage caused by CT without imposing a limit on the anticancer efficacy of chemotherapy for some who could benefit from higher doses.<sup>41,46,47</sup>

Other attempted cardioprotective strategies against chemotherapy-induced CT have included various AC analogs,<sup>48</sup> the use of liposomal and pegylated-liposomal delivery systems (which reduce capillary exchange in the myocardium),<sup>49,131,132</sup> and the use of cardioprotective agents, such as DEX.<sup>50,116</sup> While all of these cardioprotective tactics have shown benefit to varying degrees, all have logistical issues and limitations which have led to their restricted use, their reduced effectiveness, or both. Even DEX, a prodrug for an iron-chelator,<sup>133</sup> and arguably the most promising cardioprotective strategy against AC-induced CT to date, has only been approved for limited and delayed administration in adult cancer patients due to possible impairment of AC anticancer efficacy if administered too early.<sup>134-136</sup> While the practice of restricted DEX administration currently limits the utility of DEX as a cardioprotective agent for CCS, this practice is

only supported by the findings of a limited number of studies.<sup>136,137</sup> Furthermore, since these studies were published, many others have shown that there is no such risk of reduced anticancer efficacy.<sup>37,50</sup>

Although research in adult cancer survivors provides relevant evidence for the effectiveness of the aforementioned cardioprotective strategies in CCS, there is a lack of literature that has tested these strategies in the pediatric demographic directly.<sup>38,131</sup> For dose restriction, there are few high-quality studies to date that have shown the cardioprotective effectiveness of restricted dosage in CCS.<sup>38</sup> Those studies that have explored the comparative effectiveness of bolus versus continuous infusion of AC in CCS have actually shown similar cardioprotective potential between the two, and in some cases detrimental effects for continuous infusion.<sup>138</sup> For DEX, more studies have been published on its efficacy in the adult cancer patient population than have been published for CCS.<sup>139</sup> In fact, a recent review reported only low to moderate confidence for the benefit of DEX in CCS.<sup>140</sup> Conversely, the same study reported high confidence in DEX efficacy for adult cancer survivors.<sup>140</sup> However, new evidence incorporated into a recent review suggests the cardioprotective effectiveness of DEX in CCS is promising, as it has shown long-term cardioprotection without either compromising oncological efficacy or increasing the risk of secondary malignancies.<sup>138</sup>

Nevertheless, as treatment-induced CT remains a problem among long-term CCS today, the quest for an effective cardioprotective intervention continues, potentially one that will be an effective supplement to the existing effective cardioprotective strategies. Furthermore, it would be beneficial to establish a strategy for combatting CT that is equally feasible and effective across different cancer types and treatment regimens.

## V. Aerobic Exercise as a Cardioprotective Strategy

Exercise is defined as any activity that is planned, structured, repetitive, and purposeful (specifically for increasing physical fitness).<sup>141</sup> Aerobic exercise specifically, is a type of exercise that involves the use of large muscle groups for extended periods of time in activities that are rhythmic in nature.<sup>142</sup> Aerobic exercise has been shown to result in numerous physiological and functional benefits to the CV system in both the general population, and in numerous clinical populations, including HF patients,<sup>51–54</sup> coronary heart disease (CHD) patients,<sup>55,56</sup> CVD patients,<sup>57</sup> adult cancer survivors,<sup>77,78,143–145</sup> and CCS.<sup>63,64</sup> In the general population, the most well-established CV benefits of aerobic exercise training include reduced rates of cardiac morbidity and mortality<sup>57,146</sup>; reduction of CVD risk factors, which include high blood pressure, elevated non-high-density lipid levels, impaired glucose metabolism, and high BMI, among others<sup>146,147</sup>; and increase in cardiopulmonary function.

One method of assessing cardiopulmonary function is to measure CPF. Oxygen consumption at maximal exercise ( $\text{VO}_2 \text{ max}$ ), which is the maximum rate of oxygen consumption that the cardiopulmonary system is able to achieve, is often considered the gold standard outcome measure for assessing CPF. As such, maximal cardiopulmonary exercise tests (hereinafter maximal test), which are designed to reach the subject's true  $\text{VO}_2 \text{ max}$  (i.e., a plateau in  $\text{VO}_2$ <sup>148</sup>), have served as the standard against which all other tests of CPF are compared.<sup>149</sup> Technically, when a plateau in  $\text{VO}_2$  is not met, it should be referred to as  $\text{VO}_2 \text{ peak}$  instead of  $\text{VO}_2 \text{ max}$ .<sup>150</sup> However, since a plateau in  $\text{VO}_2$  is inconsistently seen during maximal testing,<sup>151</sup> and in less than half of children that complete exercise testing,<sup>152</sup> other criteria have been used to confirm that maximal effort

has been elicited during a maximal test. These include the following: failure of an increase in HR with further increases in exercise intensity; maximum heart rate ( $HR_{max}$ ) within  $\pm 10$  beats of the age-predicted  $HR_{max}$  (i.e.,  $220 - \text{age}$ ); a respiratory exchange ratio (ratio of amount of carbon dioxide produced in metabolism to the amount of oxygen consumed) greater than 1.10; a blood lactate value greater than 8 mmol/L; or a rating of perceived exertion (RPE)  $>17$  on the 6-20 scale or  $>9$  on the 0-10 scale.<sup>150,153</sup>

In instances when none of these criteria are met, the result of a maximal test should be considered  $VO_2$  peak.  $VO_2$  peak serves as an approximation of  $VO_2$  max, assuming a subject's point of volitional exhaustion is not seriously different from their true maximal effort.<sup>148</sup> Thus, both  $VO_2$  peak and  $VO_2$  max are important prognostic factors for CVD.  $VO_2$  max/peak is often expressed in relative terms (i.e.,  $VO_2$  max/peak relative to a person's body weight in kg; ml/kg/min). Predictive submaximal cardiopulmonary exercise tests (hereinafter submaximal tests) can also be used to approximate  $VO_2$  max (i.e., predicted  $VO_2$  max).<sup>149</sup>  $VO_2$  peak or predicted  $VO_2$  max, instead of a true  $VO_2$  max, are often used in clinical populations (including cancer populations) to assess CPF and CV function, since maximal tests are often too strenuous for these populations to complete properly.<sup>73-75,154 155</sup> In fact, two recent meta-analyses found that a supervised aerobic exercise intervention significantly improved post-intervention relative  $VO_2$  peak (i.e.,  $VO_2$  peak relative to a person's body weight in kg; ml/kg/min) in the adult cancer survivor population.<sup>77,78</sup> One of these reviews reported a cumulative increase of 2.90 ml/kg/min in relative  $VO_2$  peak for the intervention groups,<sup>77</sup> while the other review reported a cumulative increase of 3.13 ml/kg/min.<sup>78</sup>

Research shows that reduced CPF is an independent indicator of increased risk of CVD mortality.<sup>73</sup> For example, in a study of North American women, those with below median values for CPF experienced a much higher rate of CV death compared to those with above median values for CPF, regardless of overall risk of CVD.<sup>74</sup> A similar finding was made in a study of men who completed a treadmill exercise test, and were divided based on their VO<sub>2</sub> peak and their history of CVD. Among both those with and without previous CVD, VO<sub>2</sub> peak was the strongest predictor of mortality.<sup>75</sup> These findings are an important consideration for all cancer survivors, even those that are asymptomatic for CT, since they indicate that CPF is an important indicator of CV mortality, even in the absence of other classic symptoms of cardiac damage.<sup>69</sup>

Early studies estimated that one-third or more of the decline in functional capacity (which is related to CPF) is a consequence of physical inactivity.<sup>156</sup> However, there is also evidence to support that cardiotoxicity can affect the pumping capacity of the heart (i.e., cardiac output), subsequently diminishing CPF.<sup>157–159</sup> In their review, van Brussel et al<sup>70</sup> found that the variation in CPF deficits experienced by CCS following treatment are associated with the differences in the treatment they received, with less diminished CPF being associated with less cardiotoxic treatment. This effect has also been observed in studies by Sharkey et al,<sup>158</sup> and more recently by Christiansen et al.<sup>160</sup> This suggests that diminished CPF in CCS is caused by a combination of both the direct and indirect effects of cancer and its treatment.<sup>159</sup>

Some aerobic exercise intervention studies in clinical populations have resulted in improvements in other cardiac outcomes in conjunction with CPF. Interestingly, some of these cardiac outcomes are similar to those used to diagnose late-onset, symptomatic CT.

For example, Belardinelli et al<sup>51</sup> found that an aerobic exercise program resulted in an increase in VO<sub>2</sub> peak while also decreasing the rate of hospital readmission for HF, in HF patients. Other aerobic exercise studies have reported similar positive HF-related outcomes in conjunction with a positive effect on CPF, in the same population.<sup>54,161</sup> One study also reported an improvement in a similar cardiac measure in conjunction with an aerobic exercise-mediated increase in CPF, but in the CAD population.<sup>162</sup> These concomitant findings may provide support for an inverse relationship between aerobic exercise levels and incidence of symptomatic, late-onset CT, mediated by a change in CPF.

Other aerobic exercise intervention studies have observed decreases in established indicators of CT in conjunction with an increase in CPF. For example, in the aforementioned study by Belardinelli et al,<sup>51</sup> myocardial perfusion (i.e., an indicator of the function of the heart muscle) was also measured, and was improved due to the exercise intervention (i.e., bi- or tri-weekly 1-hour sessions of moderate intensity aerobic exercise on a cycle ergometer, for 14 months). Also, the meta-analysis by Haykowsky et al,<sup>54</sup> which concluded that an aerobic exercise program (i.e., as little as two 30-min sessions of moderate-vigorous intensity aerobic exercise, per week, for 2 months) improved CPF in the HF population, observed a concomitant increase in LVEF.<sup>54</sup> These findings are corroborated by the findings of a study in the HF population, that reported an increase in both CPF and LVEF in response to an aerobic exercise program (i.e., daily 20-minute cycle-ergometer sessions at vigorous intensity for the majority of the study).<sup>53</sup> Furthermore, aerobic exercise (i.e., thrice weekly 30+ minute recumbent bike sessions at moderate intensity, for 4 months) has been shown to simultaneously improve CPF and

LVEF in adult cancer survivors with symptomatic CT.<sup>163</sup> Unfortunately, the number of participants in this study were limited. Thus, future studies should use a controlled study design to reproduce the findings of this cancer survivor study using a larger, more heterogeneous sample, in order to support the findings of this existing study. Nonetheless, these findings offer further potential support for the CPF-mediated benefit of aerobic exercise on late-onset CT.

Altogether, studies of aerobic exercise in the general population and clinical populations, as well as one study in two adult cancer survivors,<sup>163</sup> suggest that CPF is an independent predictor of CV health for CCS. Furthermore, the correlation between CPF, certain cardiac functional parameters (e.g., myocardial perfusion, LVEF.) and common outcomes of late-onset CT (e.g., HF, CHD) seen in the aforementioned aerobic exercise studies, suggest that aerobic exercise may not only be able to improve all of these measures concurrently, but may also be mitigating the underlying CT-related damage that they all potentially indicate.

#### **a. Aerobic Exercise and CPF in Childhood Cancer Survivors**

As already mentioned, two meta-analyses have shown that CPF increases with aerobic exercise in adult cancer survivors.<sup>77,78</sup> In addition, a few reviews have shown positive results for the effect of aerobic exercise on various measures of fitness (including CPF) in CCS.<sup>64,80,81,158</sup> However, besides these few reviews, and a limited number of studies that reported CPF as an outcome<sup>164-166</sup> (in addition to echocardiographic results in once case),<sup>166</sup> the literature in CCS is still limited in comparison to what is known about the relationship between aerobic exercise, CPF and other cardiac outcomes in adult cancer survivors. To put this into perspective, no systematic review of the CCS literature



to date has been specific to the effect of aerobic exercise on CPF, or any cardiac outcome (direct or indirect) for that matter. The closest example was the recent Cochrane review by Braam et al<sup>81</sup> that evaluated the effect of a physical exercise program on any outcome of physical fitness. Unfortunately, while this review was more comprehensive in its purpose, it was consequently less concerned with exploring the specific effect of an aerobic exercise intervention on the outcome of CPF, in the population of CCS that have received a known cardiotoxic agent. This is supported by the fact that its database search strategies were not optimally specific and/or sensitive to certain concepts of this specific aim (i.e., ‘aerobic exercise’, and ‘CPF’).<sup>81</sup> Hence, the contribution of the review by Braam et al<sup>81</sup> to the field, while meaningful, does not provide any preliminary evidence of aerobic exercise’s potential cardioprotective effectiveness.

Furthermore, compared to the most recent systematic review of the adult cancer survivor literature by Beaudry et al,<sup>78</sup> which included 18 studies that reported an outcome of VO<sub>2</sub> peak, the review by Braam et al<sup>81</sup> only included four studies that reported the effect of aerobic exercise on predicted VO<sub>2</sub> max (i.e., CPF based on a submaximal exercise test).<sup>81</sup> However, this does not necessarily mean that there are no other studies that have specifically examined the effect of aerobic exercise on CPF in CCS, nor that there are no CCS studies that have used tests other than predictive submaximal tests, it may simply mean these studies have not been captured and represented in the existing meta-analyses. Overall, this gap in the review literature, and potentially the primary literature, precludes the generalization of the relationship between aerobic exercise and CPF shown in adult studies to CCS.

The lack of systematic review specifically evaluating this relationship in CCS is surprising since the deficit in CPF caused by cancer treatment in CCS has been well described in the literature.<sup>70,157,160,167</sup> Most recently, one study showed that 47% of a sample of CCS had a reduced VO<sub>2</sub> peak when compared with healthy controls.<sup>160</sup> Several other previous studies corroborate this finding, especially for CCS of ALL.<sup>70</sup> Therefore, testing the relationship between aerobic exercise and CPF in this population should be a priority, given the proven effectiveness of aerobic exercise on CPF in other populations. Furthermore, the concomitant high risk and incidence of cardiac dysfunction in CCS,<sup>9,27-29</sup> and the array of established CV benefits of aerobic exercise in other populations, provides further impetus to explore this relationship in this specific population.

## VI. Exercise Parameters and Guidelines

In all intervention research, it is important to consider how different parameters of the intervention may influence its effectiveness. For an aerobic exercise intervention, these parameters include frequency, intensity, intervention length, time per session, and modality of exercise. A recent systematic review of the structural and functional mechanisms underlying the cardiac benefit of exercise in the general population concluded that a wide variety of aerobic exercise programs, with a range of program parameters, are beneficial.<sup>168</sup> Existing exercise guidelines for the general population, such as those by the American College of Sports Medicine (ACSM)<sup>169</sup> and Health Canada,<sup>146</sup> promote minimum levels of aerobic exercise that are sufficient to elicit health benefits (e.g., improved CV health), especially in previously sedentary individuals.

Exercise guidelines associated with improved health outcomes (i.e., those by ACSM, Health Canada, the World Health Organization [WHO], and the Canadian Society for

Exercise Physiology [CSEP]) often recommend aerobic exercise at a specific dose. Dose is by definition a combination of a number of exercise parameters (i.e., frequency, time per session, and intensity), often expressed in terms of both duration per week (or day), and intensity. For example, both the WHO and the CSEP recommend a minimum of 60 minutes/day of moderate- to vigorous-intensity aerobic physical activity (PA) for individuals 5-17 years of age.<sup>170</sup> This level of PA has been shown to be associated with a reduced risk of CVD. The solidarity between organisations provides strong support for the effectiveness of 60 minutes of moderate- to vigorous-intensity exercise per day for reducing the risk of CVD in children.

The effectiveness of an exercise intervention can be affected by adherence to the prescribed program. In the past, researchers have used two main metrics to describe adherence to a specific exercise program: (1) attendance to the exercise sessions prescribed, and (2) adherence to the specific exercise intervention parameters, including frequency, intensity, and time per session. The advantage to basing exercise adherence on how well a participant adheres to pre-specified exercise parameters is that it allows the experimenter to more accurately account for any discrepancy between the prescribed exercise levels and the actual levels performed by the participants. Unfortunately, many exercise intervention studies only report adherence in terms of attendance to exercise sessions,<sup>171</sup> with high adherence being defined as attendance to 75-85% of the prescribed number of sessions.<sup>172</sup> Based on one review of exercise intervention studies in CCS, adherence levels range between 67% and 98%.<sup>64</sup> However, it was unclear or unreported whether adherence to specific exercise parameters was used to establish these percentages.<sup>64</sup> In all cases, this tendency to report attendance instead of adherence to

specific parameters may be due to the burden on the experimenter, the participants, or both.

## VII. Exercise Recommendations for Childhood Cancer Survivors

There are few consensus-based PA recommendations/guidelines for CCS that have been published to date, and none that are considered PA standards of care. Most recently (in 2015), a group of 27 international authors developed the Pediatric Oncology Exercise Manual (POEM), which contains a set of aerobic exercise recommendations for CCS.<sup>69</sup> These recommendations are based on the health benefits of exercise for CCS, including the benefits against some of the late effects of common cancer treatments for pediatric cancers (i.e., CVD, osteoporosis, reduced quality of life, fatigue, etc.).<sup>63,64,173,174</sup> These recommendations were fairly broad in their prescription; 20-70 minutes of moderate-vigorous aerobic exercise, 2-5 times/week, for at least 12 weeks.<sup>69</sup> The objective of these PA recommendations according to POEM is specific to each phase of treatment (i.e., induction, consolidation, maintenance/post-remission, and survivorship).<sup>69</sup> However, the objective during all phases indirectly encompasses mitigating a decrease in CPF.

Other recommendations have gone so far as to prescribe exercise that is specific to the current cardiac status and past cardiotoxic treatment exposure of CCS,<sup>175</sup> with the higher risk group receiving a higher degree of supervision and a mandated pre-exercise assessment. While this approach is promising, especially considering the authors planned to review and amend recommendations every two years, it is unclear which outcomes were involved in the review, and whether any subsequent decision on amendment ever occurred. Other publications are in support of PA being recommended to CCS, and also promote screening survivors that are at higher risk of adverse events related to exercise,

such as echocardiography for survivors exposed to AC and/or mediastinal radiation, and musculoskeletal examination for all survivors. However, none of these publications specifically outlined PA recommendations.<sup>63,176</sup>

Despite how broad the recommendations by POEM are, they provide the most specific benchmark for exercise prescription in this population. It is also important to note that compared to the range of doses of aerobic exercise included in existing PA guidelines for healthy children (i.e., 150-300 minutes/week, moderate-vigorous intensity),<sup>170,177,178</sup> the POEM recommendations either promote a dose that is equal to, or lesser than the low end of this range. This difference addresses a unique exercise concern of CCS, namely, the increased potential for adverse effects of exercise (e.g., increased exercise may increase the likelihood of infection in CCS because blood cell counts are lower due to certain treatments).<sup>69</sup>

The editors of POEM clearly considered the evidence on the benefits of aerobic exercise against treatment-related CVD when designing their recommendations. Unfortunately, the evidence they used to inform their recommendations, and consequently optimize the recommendations to protect CCS from treatment-induced CVD, was still limited in a number of ways. For instance, all of the studies referenced in this manual only tested the effectiveness of a single aerobic exercise intervention on health-related outcomes,<sup>69</sup> meaning none directly compared the relative effectiveness of two or more different exercise programs, each with a unique combination of exercise parameters. For example, most of the studies referenced only tested the effectiveness of 50-60 minutes of aerobic exercise per day.<sup>69</sup> While this is a widely recommended and recognized session duration to elicit health benefits in children in the general population,

it may not be the most effective session duration for CCS. The same applies to other parameters of aerobic exercise as CCS have specific limitations to exercise, including treatment-induced functional impairments,<sup>157</sup> risk of adverse effects,<sup>69</sup> and organizational barriers,<sup>171</sup> that may consequently impact the effectiveness of traditional guidelines.

## VIII. Summary and Purpose

In summary, treatment-induced CT in CCS is a serious and widespread issue that can increase the risk of CVD later in life. Since these cardiotoxic cancer therapies are mainstays of cancer medicine, it is essential that a strategy to protect the heart be determined. Optimally, any new strategies should supplement the existing cardioprotective strategies known to be effective. Based on the already known cardiac benefits of exercise in the general population and relevant clinical populations, it is possible exercise could also serve to prevent or reduce AC-induced CT in CCS, via an increase in CPF.<sup>179</sup> Therefore, the main purpose of this review was to search the literature systematically for all studies that have examined the effect of an aerobic exercise intervention on CPF in CCS treated with a known cardiotoxic agent, and to pool the results of these studies for analysis. More specifically, the primary aim of the review is to answer the following review question: “What is the effect of aerobic exercise on CPF in CCS treated with a known cardiotoxic agent when compared to usual care?”

The specific objectives of this review were to determine the moderating effect of the following independent variables on CPF, in CCS: aerobic exercise modality; intervention length; exercise intensity; exercise session frequency; duration per session; reported adherence levels to the exercise intervention; treatment status (i.e., exercise during versus exercise following treatment); time since diagnosis (i.e., early-onset versus late-onset

CT);<sup>105</sup> primary cancer diagnosis; primary cancer treatment(s); and the dose of aerobic exercise prescription, relative to the current established recommendations for CCS in the POEM (i.e., below range, within range, or above range).<sup>69</sup> In other words, the secondary aim of this review is to answer the following question: “Are there any moderating variables for the effect of aerobic exercise on CPF in CCS treated with a known cardiotoxic agent, when compared to a control group receiving usual care?”

## Chapter 3: Methodology

### I. Criteria for Considering Studies for this Review:

#### a. Types of Studies

All studies included in this review needed to be either a randomized controlled trial (RCT) or a controlled clinical trial (CCT). In addition, only studies with English language reports/articles were included in this review, due to a lack of funds and personnel available to interpret other languages.

#### b. Types of Participants

Studies included in this review exclusively included participants that were diagnosed with cancer at the age of 19 or younger, which includes childhood and adolescence (hereinafter “childhood”). Studies included in this review included participants who were currently receiving, or had at some point received, some form of cardiotoxic cancer treatment.<sup>122</sup> For studies that included some participants who were currently receiving/previously received a known cardiotoxic treatment and other participants who were not or had not received any therapy, the majority (>50%) of participants must have been currently receiving/previously received a cardiotoxic treatment for the study to be eligible. These eligibility criteria were chosen to both reduce between-study heterogeneity in the included studies, as well as target studies that most closely address the review question.

#### c. Types of Interventions and Comparisons

Only studies that included at least one intervention group that received some form of aerobic exercise intervention (EX), and a control group not given any exercise program (i.e., a ‘standard of care’ control group; CON), were deemed eligible. A CON group



qualified as a standard of care group when the group had in some way been asked not to change their current exercise behaviours (i.e., by increasing or decreasing their current levels of exercise), or had made a decision not to change their current exercise behaviours. The former applies to RCTs, while the latter applies to CCTs, in some cases. This eligibility restriction limited the review to studies that showed the ‘uncontaminated’ intervention effect of exercise, as well as reduced the amount of between-study heterogeneity in the included studies. Contamination refers to the effect of giving a control group a substitute for the exercise program, such as exercise material, health information, or a progressive stretching routine (i.e., an attention-control group), on the observed intervention effect.<sup>159</sup> The rationale for this eligibility criterion was to reduce between-study heterogeneity in the included studies.

#### **d. Types of Outcome Measures**

##### **i. Main outcome for ‘Summary of Findings’ table**

CPF and relative VO<sub>2</sub> peak were the principal outcomes considered for the ‘Summary of Findings’ table. This outcome was chosen primarily to enable comparison with the findings from previous similar reviews in adult cancer survivors.<sup>77,78</sup> In order for studies to be deemed eligible for this review, CPF needed to be determined via either a maximal aerobic protocol (i.e., Godfrey protocol, Bruce treadmill protocol, other maximal graded protocol) or via a predictive submaximal aerobic protocol (i.e., 20-minute shuttle test, and 9-minute run-walk test).

Also, the included studies that used a maximal protocol and reported VO<sub>2</sub> peak were only deemed eligible for this review if it was explicitly stated that exercise testing was completed to volitional exhaustion. Meanwhile, an additional condition for the studies

that used a submaximal test to estimate CPF was that the test must have been previously validated for the current age of the cohort being tested. It should also be noted that although some of the protocols are considered submaximal, they may still require a near-maximal effort.<sup>180</sup>

## II. Search Methods for Identification of Studies

### a. Electronic Database Searching

Based on a similar review of the adult cancer population<sup>77</sup>, as well as what was done in other related Cochrane reviews,<sup>139,181–186</sup> the following electronic databases were searched for potentially eligible (PE) studies. Each database has an appendix that includes the specific search terms that were used to search it.

- MEDLINE/PubMed (**Appendix I**)
- CENTRAL (**Appendix II**)
- EMBASE/Ovid (**Appendix III**)
- Web of Science (**Appendix IV**)
- CINAHL (**Appendix V**)
- SPORTDiscus (**Appendix VI**)
- ProQuest Digital Dissertations (**Appendix VII**)
- Physiotherapy Evidence Database (PEDro) (**Appendix VIII**)

### b. Grey Literature Searching

In addition, multiple ‘grey literature’ sources (i.e., conference proceedings/agendas and other non-peer-reviewed sources) were searched for PE studies. One group of these sources were the various websites of appropriate conferences, organizations, and associations that were not indexed in any of the searched databases. Some of the organizations and associations were chosen for this search strategy since they had been cited as providing financial support for one or more of the PE studies retrieved through electronic database searching. All websites were specifically searched for conference

proceedings/agendas (hereinafter “conference proceedings”), abstracts, and/or reports of studies not previously identified through electronic database searching. The websites of the following conferences, organizations, and/or associations were searched:

- American Institute for Cancer Research
- American Cancer Society
- Canadian Cancer Research Conference
- Danish Cancer Society
- Dutch Cancer Society
- German Josep Carreras Leukemia Foundation
- National Cancer Institute, Division of Cancer Control & Population Studies

These websites were initially searched for all of the aforementioned types of PE reports by starting at the website’s homepage, and searching through all relevant links cited on this page. In cases where this led to individual PE results (e.g., abstracts and/or reports of studies), these were moved forward in the screening process. Alternatively, in cases where this led to PE results that needed to be filtered further (e.g., conference proceedings), this was done using multiple, single keyword searches, via the “find” function in Google Chrome. Specifically, for these websites, keyword searches included terms associated with the specific review concepts (i.e., "exercise", "activity", and "children"). However, if searching yielded neither individual PE results nor conference proceedings, an advanced Google search was performed on the website itself, using simple keyword searches (two words max).

It should also be noted that in addition to using the “find” function in Google Chrome for further filtering conference proceedings, and in some cases the advanced Google search of websites, there were a few cases that required a basic Google search for relevant conference proceedings, since both aforementioned search strategies yielded no results. These included one basic Google search for the American Institute for Cancer

Research (i.e., “american institute for cancer research conference proceedings”), and another for the Dutch Cancer Society (i.e., “exercise dutch cancer society conference”). The complete list of search strategies and associated search terms for searching these websites are included in **Appendix IX**.

Other sources of grey literature that were also searched for PE studies included Google Scholar and the WHO International Clinical Trials Registry Platform (ICTRP). While Google Scholar was searched for any reports of a PE study, such as an abstract, a full-text report, or a conference proceeding, the WHO ICTRP was specifically searched for ongoing trials. Specific key word combinations, and relevant individual key words were used to search WHO ICTRP and Google Scholar, respectively. The specific search terms used to search both of these sources can also be found in **Appendix IX**.

### **c. Additional Search Strategies**

A number of additional search strategies were also completed in order to identify further PE trials, including: (1) cited reference searching for any published reports associated with eligible studies, using the features in Web of Science, and Google Scholar; (2) using the PubMed “similar articles” function for all eligible studies; (3) screening the reference lists of relevant reviews and eligible studies retrieved using the aforementioned search strategies; and (4) contacting first authors of the included studies, studies that met all but 1 or 2 eligibility criteria, and studies for which a judgement was not possible based on the information provided within the retrieved reports.

Lastly, hand-searching, which is a manual examination of each article in a journal issue to identify additional PE trials, was completed for all existing issues of the “World Journal of Meta-Analysis”, from inception to present. This search strategy was completed

since this journal was not completely indexed in any of the searched databases, and it was determined to be a potentially important source of eligible studies due to one relevant review being published in it.<sup>78</sup>

Although searches were not restricted to English language trials, no translator was recruited to assist with this review, and therefore no formal translation of non-English language trials was possible. Therefore, in some cases, when it was not possible to determine whether a study was eligible based on the part of its report that was in English (and/or in some cases the non-English parts of its report), the study was excluded.

### III. Study Selection

The following section provides the specific steps encompassed in the narrowing of the initial results of each search strategy, and ultimately leading up to the inclusion of eligible studies in the review. Each sub-section lays out the specific steps included in each search strategy.

#### **a. Electronic Database Searching**

The initial step in the narrowing of results from electronic database searching was the removal of all duplicate citations from the total set of electronic database citations, using RefWorks software (also known as the ‘deduplication’ step).

The next step included one author (AB) evaluating all remaining reports of studies (i.e., records) by screening their titles and abstracts (first screening stage), and subsequently judging whether or not they were PE. The first screening stage also included re-screening and judgment of the same records by a second author (MK). Any

disagreements between the two authors after this screening stage were resolved through discussion.

The final step in screening the records from electronic databases included retrieval, and screening of the full-text reports of all remaining PE references (second screening stage). It should also be noted that at this stage, multiple reports of the same study were linked together (i.e., labelled as multiple publications of the same study) based on the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (hereinafter Cochrane Handbook).<sup>187</sup> The second screening stage was performed by three authors (AB, MK, and SG), with the help of a standardized form, known as an ‘inclusion assessment form’ (**Appendix X**), plus an instruction sheet for assessing eligibility using this form (**Appendix XI**). This form was designed for the current review specifically, based on an inclusion assessment form template included in the “Guide for developing a Cochrane protocol” produced by the Cochrane Public Health Group,<sup>188</sup> and with eligibility criteria sequenced in order of importance. A single failed eligibility criterion mentioned on this form was sufficient for exclusion of the study. On the other hand, the studies that met all eligibility criteria included on this form were selected to be included in the review. Any disagreements between the three authors on judgement for a particular study, were resolved by consensus.

#### **b. Grey Literature Searching**

The steps used in narrowing the results from grey literature searching were almost the same as the steps used for the electronic database results. The two differences were: (1) the deduplication step was not completed for the results retrieved from grey literature sources; and (2) both screening stages were only completed by a single author (AB). The

reason the deduplication stage was not completed is that it was deemed impractical given the lack of methodology for efficiently exporting the citations from all grey literature sources. Furthermore, time and personnel available for hand-searching for duplicates was lacking, not to mention hand-searching for duplicates would have been redundant given all the same grey literature citations were also hand-searched during the first screening stage. The reason only one author (AB) was responsible for screening and judging these results at both screening stages was that there was a lack of time and personnel available to complete these tasks in a timely manner.

### **c. Additional Search Strategies**

For all additional search strategies, only one author (AB) completed the screening and judgement tasks at both screening stages, due to lack of available time and personnel. Beyond this, the screening steps employed for the five separate, additional search strategies, were varied. For instance, while deduplication and both screening stages were completed for the reference list search results, the deduplication stage was not completed for any of the other additional search strategies. Furthermore, almost all additional search strategies completed a primary screening stage, with the exception of contacting authors since it was deemed unnecessary given how few results were retrieved directly from authors. **Table 1** details the stages included in the respective screening processes for each additional search strategy.

**Table 1: A detailed description of screening stages completed for each additional search strategy**

<b>Additional Search Strategy</b>	Deduplication stages completed	1 <sup>st</sup> screening stage completed	2 <sup>nd</sup> screening stage completed
Reference lists	✓	✓	✓
“Similar Articles”		✓	✓
Cited reference searching		✓	✓
Hand searching		✓	✓
Contacting authors			✓

#### IV. Data Extraction and Management

Once all eligible studies were identified, relevant information and data were independently extracted from all reports associated with all eligible studies. This was done by one author (AB) due to lack of available time and personnel. Extraction was completed using a ‘data extraction form’ customized for this review, and designed based on information provided in chapter 7.5.3 of the Cochrane Handbook,<sup>187</sup> as well as templates included in the “Guide for developing a Cochrane protocol”.<sup>188</sup> The data extraction form included the following items (within one of seven general categories) in an excel spread sheet:

1. **General publication information:** first author, citation, publication date, country, funding source of study, and duplicate publications.
2. **Study characteristics:** specific study design (i.e., RCT or CCT), response rate, time point of randomisation (if relevant), aims/problem addressed by intervention, setting of intervention, study dates (i.e., start and end), recruitment location and



method, providers of intervention, inclusion and exclusion criteria, strategies to address diversity and/or disadvantage (possible sources of diversity and/or disadvantage in the population which may have resulted in some groups being over- or under-represented in the sample include all socio-demographic characteristics: place, race, occupation of guardian, gender, religion of guardian, education of guardian, socioeconomic status, and social status),<sup>188</sup> number of intervention groups, time points measured, duration of follow-up, intention-to-treat analysis, statistical methods, power calculations, and sustainability of intervention mentioned and/or considered.

3. **Participant characteristics:** age, gender, ethnicity, co-morbidities, primary cancer diagnosis, type of treatment (total cumulative dose, length of treatment, combination), treatment status (i.e., during treatment or completed treatment), duration since initial diagnosis and/or initiation of treatment, baseline exercise/PA levels, anthropometric measurements (i.e., height, weight, BMI, sum of skinfolds), number of participants (recruited, allocated, and evaluated) for each group, completion percentage for each group, number and reasons for exclusions from intervention or control group, and participants lost to follow-up (with reason, if reported).
4. **Interventions:** exercise program parameters (modality, duration, frequency, time per session, intensity, and total volume), setting of exercise intervention, level of aerobic exercise relative to current childhood cancer recommendations,<sup>69</sup> other interventions, and standard care description for control group.

5. **Primary outcome data:** specific exercise test used, diagnostic criteria for completion of test, VO<sub>2</sub> peak data, submaximal test data, whether final scores or change scores from baseline are reported, unit of measurement, and time points reported.
6. **Secondary outcome data (*including all possible secondary outcome measures*):** levels of biomarkers of CT (e.g., cardiac troponin), levels of biomarkers of cardioprotection (e.g., antioxidants), results of echocardiographic analysis, multigated acquisition scanning, or other cardiac scanning (e.g., LVEF, fractional shortening, ventricle dimensions, myocardial perfusion, etc.),<sup>117,118,122</sup> cardiac morbidity risk, cardiac mortality risk, body composition, quality of life (QoL), immune profile, muscle strength, cancer control, exercise/PA levels, range of motion (ROM), flexibility, fatigue, pulmonary function, anaerobic capacity, adherence (overall and for separate parameters), both exercise- and inactivity-related adverse events (e.g., reduced cancer treatment effectiveness, increased incidence of cancer-specific events, increased incidence of cardiac-specific events, and injury because of exercise), cost-effectiveness, and time points reported for any secondary outcome measures.
7. **Potential risk of bias:** sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias (listed below in section V.a).

## V. Data Analysis

### a. Assessment of Risk of Bias in Included Studies

Following the extraction of all data and relevant information from the included studies, one of the first data analysis steps was assessing the risk of bias in each included study. Again, this was completed by only one author (AB) due to lack of available time and personnel. First, risk of bias for each study was assessed for the following individual domains:<sup>187</sup>

1. **Random sequence generation:** whether the method used to generate the allocation sequence was sufficient to allow the groups to be comparable, by avoiding possible self-selection (this reflects risk of ‘selection bias’).
2. **Measures to conceal allocation:** whether the intervention allocation could have been foreseen, before or during recruitment, by participants or researchers, or changed after assignment (this reflects risk of ‘selection bias’).
3. **Blinding of outcome assessment:** measures that were used to blind outcome assessors from knowledge of which intervention a participant had received, and whether it was effective or not (this reflects risk of ‘detection bias’).
4. **Incomplete outcome data:** the completeness of data for the primary outcome, including attrition and exclusions from analysis; also whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions (where reported), and whether any re-inclusions in analyses were performed by review authors (this reflects risk of ‘attrition bias’).

5. **Selective reporting:** the possibility of selective outcome reporting and how this was examined by the review authors (this reflects risk of ‘reporting bias’).
6. **Other sources of bias:** any other important concerns about bias not addressed in the other domains (i.e., ‘publication bias’; ‘small-study effects’; potential conflict of interest; representativeness [aka difference between sample participants and true population of interest]; age-matched validation of the outcome/tool/protocol; reliability of the outcome/tool/protocol; lack of power; differences in excluded participants; and comparability of groups following randomization [aka baseline imbalance]).

One domain that was not included in the assessment of risk of bias is ‘blinding of participants and personnel’ (which reflects performance bias), since this is generally speaking not a practical criterion for exercise intervention trials. It is important to acknowledge that lack of blinding of participants may have introduced some ‘performance bias’ into the included exercise studies, which is the systematic difference between groups due to some elements of the treatment received by the intervention group that was unrelated to the intervention of interest. An example of a potential performance bias is the placebo effect on participants receiving an exercise intervention due to the increased attention they receive from the supervisory personnel. Unfortunately, this bias was unavoidable due to the nature of exercise intervention research.<sup>159</sup>

All information from included trials used to assess risk of bias in the above domains consequently informed a judgement of either “low risk of bias”; “high risk of bias”; or “unclear risk of bias” for each individual domain, according to the directions described in the Cochrane Handbook.<sup>187</sup> In brief, judgements on risk of bias for each individual

domain were made by comparing the available information from the retrieved reports to the lists of common examples of either high or low risk of bias provided in ‘Table 8.5.d’ of the Cochrane Handbook.<sup>189</sup> In cases where a clear match could be made between what was said about one of the studies and what was written in one of the lists, the study was judged at either high or low risk of bias for that particular domain. In cases where a clear match could not be made, that domain was judged at unclear risk of bias. For instance, some of the common examples of low risk of bias for random sequence generation was “referring to a random number table”, “using a computer random number generator”, and “coin tossing”.<sup>189</sup>

Furthermore, these individual domain judgements were combined to yield an overall risk of bias judgement for each included study, using the following cut-offs: 1) high overall risk of bias: >1 high risk of bias judgements (for one domain) OR > 4 unclear risk of bias ratings; 2) unclear risk of bias:  $\leq 1$  high risk of bias judgements AND  $\leq 4$  unclear risk of bias judgements; and 3) low risk of bias: 0 high risk of bias judgements AND <4 unclear risk of bias judgements. It should be noted that since there was no specific guidance or standard regarding cut-offs for overall risk of bias after combining individual domain judgements, these cut-offs were chosen so as to err on the side of overestimating risk of bias.

Primary analysis of findings included all studies, regardless of risk of bias judgements. Meanwhile, one of the sensitivity analyses compared the outcome of including all studies in a meta-analysis with the outcome of only including those studies that received an overall low or unclear risk of bias judgement.

It is also important to note that the individual domain risk of bias judgements were not blinded due to lack of resources (i.e., time and personnel). Furthermore, since resource limitations precluded multiple researchers from completing the risk of bias assessments, consensus on both the interpretations of risk of bias domains, and the judgements of risk of bias, were not possible. Instead, in order to verify that the single author responsible for judging risk of bias (AB) had a clear and accurate interpretation of the items and their operationalization, an expert in systematic reviews (specifically, Cochrane reviews) was consulted.

### **b. Dealing with Missing Data**

Before proceeding with analyses of the data extracted from the included studies, it was necessary to deal with which data were missing from some of these studies. The review dealt with missing data differently depending on its source. The approaches used for dealing with each source of missing data encountered in this review are discussed below.

#### **i. Whole studies missing from a review**

Measures were taken to avoid ‘publication bias’ in the findings of the review. These measures included searching a variety of “grey literature” sources for unpublished reports of PE studies (as previously described). Although there is reluctance among other meta-analysts and journal editors to include unpublished reports in meta-analyses,<sup>190</sup> including them is the most obvious way to avoid publication bias. The importance of including these reports is stressed by the results of the meta-analysis by Hopewell et al,<sup>191</sup> which determined that excluding unpublished reports may account for a difference in an intervention effect of up to 9%. Furthermore, direct communication with authors was

used to help identify any other currently ongoing, or unpublished study findings that were not retrieved from any of the grey literature sources.

ii. Missing Outcomes or Missing Summary Data/Statistics

Since one of the eligibility criteria for study inclusion in this review was the reporting of CPF as an outcome measure, data for this outcome of interest could not be missing for any included studies. That being said, in some cases these data were retrieved directly from authors instead of from a published report. Similarly, in cases where one or more of the review's secondary outcomes was mentioned in either the aim of a study, or in the study's protocol (or both), but the data for this outcome was missing from the study's report(s), retrieval of these data was attempted via searching of trial registries; and/or searching of other related published articles. In cases that the missing data were found using one of these methods, this study was judged at high risk for reporting bias. Alternatively, when any of the above mentioned data could not be retrieved through any of these methods, it was judged at either high or unclear risk for reporting bias, depending on whether or not data for the primary outcome had been extracted from a report or retrieved directly from an author, respectively.

In some cases, the CPF change scores reported for an included study were missing standard deviation (SD). A few approaches were used for dealing with these missing values. The initial approach involved determining whether there were any other statistics reported for the given study that allowed for the calculation or estimation of the missing SDs. These could have included confidence intervals [CI's], standard error [SE] values, t-values, p-values, and/or F-values for the differences in change scores.<sup>187</sup> In cases when none of these values were reported for the given study, the average value of the SDs

reported by the other included studies was imputed. ‘Sensitivity analyses’ (defined in **section VI.b**) were also used to assess the effect of changing the imputed value (for those studies that required imputing) to some other SD value reported among the included studies (i.e., the highest SD reported by the included studies, and the lowest SD reported by the included studies).<sup>187</sup>

### iii. Missing Participants

In cases where included studies reported some drop-out/attrition (i.e., missing participant data), all collected and reported data were extracted, yielding “available case analysis” results for these studies. For all other studies, it was assumed that data for all participants were included in calculations, and thus intention-to-treat results were available. It should be noted that in one study that reported results for both intention-to-treat analysis and pre-protocol analysis, intention-to-treat analysis was chosen. While the data from all studies were treated the same during meta-analyses, regardless of the type of analysis it informed, the impact of the missing data for one or more participants from certain studies were accounted for in the assessment of risk of bias for these studies (specifically, the “incomplete outcome data” domain).

### c. Measures of Effect Estimate

Two main random-effects meta-analyses of the collected CPF data were performed, using inverse-variance weighting. Inverse-variance weighting allocates a weight to each study by dividing its effect estimate by the square of the SE (i.e., the variance). This resulted in the effect estimates of those studies with higher SDs having a lower bearing on the overall effect (since they must divide their effect size by a larger variance).

Random-effect meta-analysis was chosen over fixed-effect meta-analysis *a priori*,



because it was suspected (based on substantive knowledge of the area) that the included studies would represent more than one distribution. In other words, it was suspected that the individual effect estimates of the included studies would not all be from a single distribution, but would be estimates of effects from different distributions, each distribution being for a distinct clinical population. The two main meta-analyses conducted included: (1) a meta-analysis of all studies, using the outcome of CPF; and (2) a meta-analysis of studies that used a maximal test, using the outcome of VO<sub>2</sub> peak.

Given the heterogeneity of the CPF assessment methods and in an effort to standardize the different units of measure, the first step for the first main meta-analysis was converting the results of all the exercise tests to *% change scores*. Depending on what information was provided and/or retrieved for the study, either **Equation 3.1** (when both baseline and post-intervention values were reported) or **Equation 3.2** (when change score was directly reported) were used to convert to % change score.

$$\% \text{ change score} = \frac{\text{post-intervention value} - \text{baseline value}}{\text{baseline value}} * 100\% \quad (3.1)$$

$$\% \text{ change score} = \frac{\text{change score}}{\text{baseline value}} * 100\% \quad (3.2)$$

After this step, the steps for both main meta-analyses were approximately the same. The first of these was calculating the mean differences (MDs) of each individual study included in the given meta-analysis. For the first main meta-analysis, this included combining each pair of % change scores from each study, calculated using **equations 3.1** and **3.2** (one pair per study, and one % change score per group). Combining these yielded the mean difference in % change scores for each study (%MD; the difference between the % change scores of the control and intervention groups in each study). This was done

using **equation 3.3** below. In this equation, (I) denotes the % change score for EX, and (C) denotes the % change score for CON.

$$\%MD = \% \text{ change score (I)} - \% \text{ change score (C)} \quad (3.3)$$

A similar step was performed for the second main meta-analysis (i.e., calculating MDs for the individual studies), using a slightly modified version of **equation 3.3**, where % change scores were replaced by absolute change scores (for both EX and CON). These changes yielded the MD for each study, not to be confused with the %MD.

The second step for both main meta-analyses included combining the individual MDs, to yield pooled effect estimates. As already stated, pooling for both meta-analyses was completed using inverse-variance weighted MDs. For the first main meta-analysis, individual %MD values were weighted and pooled to calculate the pooled %MD for all of the included studies (i.e., %MD<sub>pooled</sub>). This was done using **equation 3.4**. In this equation, the subscript “i” denotes the number of the study, and the subscript (IV) denotes that the value has been weighted using inverse variance.

$$\%MD_{\text{pooled}} = \sum_{i=1}^n \%MD_{i(IV)} \quad (3.4)$$

Again, a slightly modified version of the same equation used for the first main meta-analysis was used for the second main meta-analysis. In this case inverse-variance weighted %MD values in **equation 3.4** were replaced by inverse-variance weighted MD values.

The final step to both main meta-analyses was using the SEs of all studies included in each respective meta-analysis to derive a CI and a p-value. The latter indicates the

strength of the effect of aerobic exercise on CPF, across studies, and whether the CI is compatible with random variation, or whether it is large enough to indicate inconsistency of intervention effects across studies.<sup>187</sup>

Since data for secondary outcome measures were limited, and less than half of the reported secondary outcome measures were reported in more than one of the included studies, no meta-analyses were conducted for these.

#### **d. Assessment of Heterogeneity**

Any variability, with respect to any study characteristic (e.g., specific participant characteristics, intervention parameters, intervention setting, timing of intervention, etc.), among the studies included in a systematic review or meta-analysis may be termed ‘heterogeneity’. However, for the purposes of simplification, heterogeneity in this review only refers to variability in the intervention effects reported by the studies included in this meta-analysis, as was suggested by the Cochrane Handbook.<sup>187</sup> For the purposes of this review, sources of heterogeneity broadly included differences in participants and differences in interventions, which are both termed clinical diversity. Any differences in study design were assumed to have affected the risk of bias (i.e., methodological diversity) and not the heterogeneity, and therefore were not accounted for by the heterogeneity statistics, which are discussed below.

In this review, between-study heterogeneity was assessed in both main meta-analyses using the chi-square ( $\text{Chi}^2$ ) test, with a significance level at  $p\text{-value} < 0.1$ .<sup>187</sup> Heterogeneity was then quantified in both main meta-analyses using the  $I^2$  statistic, with

$I^2 < 50\%$  indicating moderate heterogeneity, and  $I^2 \geq 50\%$  indicating substantial/considerable heterogeneity.

Beyond assessing its presence, a few potential sources of heterogeneity were examined in this review, via meta-analyses known as ‘subgroup analyses’. The first subgroup analysis was for intervention length. The two main reasons intervention length was assessed as a potential source of heterogeneity are that it has previously been associated with changes in the effectiveness of an exercise intervention on CPF, in both the general population and other (similar) populations;<sup>192</sup> and the included studies could be evenly divided into two subgroups based on this factor. It is important to note that although studies were divided into two subgroups for analysis (i.e., intervention length  $\leq 3$  months vs. intervention length  $>3$  months), the cut-off for subgroups was not pre-determined, as the aim was not to explore a specific cut-off, but rather to explore whether intervention length itself was a moderating factor.

Unfortunately, none of the other primary exercise parameters (i.e., intensity, duration per session, frequency, aerobic exercise modality, and total volume), nor the reported adherence levels to the exercise program, could be assessed as potential sources of heterogeneity. The main reasons these parameters could not be assessed included one of the following: (1) inconsistent/minimal reporting across all included studies (i.e., aerobic exercise modality, and adherence); (2) the parameters could not be used to evenly divide the studies into two homogeneous subgroups (i.e., aerobic exercise modality, intensity, and frequency); (3) the majority of studies fell within the range of POEM recommendations for CCS (i.e., intensity, duration per session, and total volume); and

most importantly, (4) there were too few included studies to yield a reliable result for all of these subgroup analyses.

Only one treatment-specific variable was assessed for its influence on heterogeneity: treatment status (i.e., majority of participants receiving treatment vs. majority of participants completed treatment). The reasons treatment status was assessed as a potential source of heterogeneity are the same as those for intervention length. Unfortunately, subgroup analyses for other treatment- and disease-specific variables could not be completed. The reasons for not performing these subgroups analyses were mostly the same as those for not completing the exercise parameter-specific subgroup analyses, except for reason (3).

Two *post hoc* subgroup analyses were also developed after completing data extraction, due to the identification of two other potential sources of heterogeneity, for which the included studies could be evenly divided into two subgroups. These included subgroup analyses of ‘studies that used a maximal test vs. studies that used a submaximal test’, and ‘studies that used exercise tests validated/used in an age-matched population vs. studies that used exercise tests not validated/used in an age-matched’.

All subgroup analyses were assessed using the test for subgroup differences in RevMan software, which yielded a  $\text{Chi}^2$  statistic with a significance level, as well as an  $I^2$  statistic. Significant  $\text{Chi}^2$  statistics ( $p\text{-value} < 0.1$ ) indicated a significant difference between subgroups, and are evidence of the given variable being a significant source of heterogeneity between the included studies.<sup>187</sup> The  $I^2$  statistic on the other hand was used to quantify the amount of heterogeneity that could be attributed to the given variable

being tested in the subgroup analysis, using similar cut-offs for “moderate” and “substantial-considerable” as were used for the main test of heterogeneity. The results of these subgroup analyses form the basis for addressing the specific objectives of this review, namely determining how different sources of clinical diversity contribute to the effect of aerobic exercise on CPF).

#### **e. Assessment of Reporting/Publication Biases**

Although several measures were used to avoid reporting bias and/or publication bias, including all measures included to avoid/deal with missing data (i.e., missing studies), missing outcomes, missing SDs, and missing participants, it is still possible that either or both types of bias was present in the review findings. Therefore, funnel plots (i.e., plots of SE vs. intervention effect estimate, with SE on a reversed scale on the y-axis) were completed, both for all included studies, and for the maximal test studies. SE was used in the funnel plots instead of total sample size, since it is better able to summarize other relevant factors for determining the statistical power of a study (i.e., SD for continuous outcomes).<sup>193</sup> These plots were used to assess whether smaller studies, and presumably less precise studies, showed more pronounced beneficial effects than larger studies (i.e., small-studies effects, a potential form of publication bias). If small-study effects have affected the sample of studies used in the review, this will be visually represented in the funnel plot, in the form of asymmetry.<sup>187</sup> A funnel plot may display small-study effects due to either publication bias, or other reasons, such as low methodological quality/rigour in small studies.<sup>187</sup>

In addition to funnel plots, the linear regression analysis approach to quantitatively test for the presence of small-studies bias, as described in Egger et al.,<sup>194</sup> was used to help

support the findings of the funnel plots. Most importantly, the guidance included in Egger et al.,<sup>194</sup> states that a negative y-intercept may indicate the presence of small-studies bias. It is very important to remember that even when a funnel plot test does not provide evidence of asymmetry, publication bias can still be present, and this may or may not be indicated by linear regression analysis, depending on whether or not small studies are disproportionately associated with publication bias, respectively.

#### **f. GRADE Scoring of Quality of Evidence**

The quality of evidence on the effect of aerobic exercise on CPF in the included studies was graded according to the GRADE approach outlined in the GRADE handbook.<sup>195</sup> In brief, the GRADE approach is based on discrete judgements for the following factors that are related to the quality of the existing evidence (from the included studies) for the outcome of interest: (1) study design; (2) risk of bias; (3) inconsistency between studies; (4) indirectness of evidence; (5) imprecision of the pooled effect estimate; (6) publication bias; (7) large magnitude of effect; (8) dose-response gradient; and (9) effect of plausible residual confounding (i.e., unaccounted for determinants of outcome). According to the GRADE approach, these discrete judgements were combined by either downgrading (for factors 1-6) or upgrading (for factors 7-9) the quality of evidence by one or more levels, in order to yield a final overall judgement (i.e., very low, low, moderate, or high quality of evidence).

## **VI. Data interpretation**

When interpreting the analyzed data, four main questions were considered for the primary objective and each specific objective, individually. The questions were as follows:

1. What is the direction of the effect of an aerobic exercise program? (Is the positive change in CPF or VO<sub>2</sub> peak in favour of the intervention group or the control group? Is it in favour of one or more specific subgroups [i.e., one of those assessed in one of the subgroup analyses]?)
2. What is the size of the effect of an aerobic exercise program? (Is it statistically significant [p-value < 0.05]? Is it clinically significant [MD in relative VO<sub>2</sub> peak >1 ml/kg/min]?<sup>196–198</sup>)
3. Is the effect consistent across studies of aerobic exercise programs? (How much between-study heterogeneity was there among the included studies or among the studies in a single subgroup?)
4. What is the strength/quality of evidence for the effect?

The results of the meta-analyses and subgroup analyses provided answers to questions 1 and 2, and the results of the heterogeneity assessments provided an answer to question 3. Meanwhile, question 4 relied on the overall judgement on quality of evidence based on the GRADE approach.<sup>195</sup>

#### **a. Subgroup Analyses and Investigations of Heterogeneity**

As already mentioned, the heterogeneity in the included studies was investigated via subgroup analyses for intervention length, treatments status, type of exercise test, and prior validation/use of exercise test used. Since subgroup analyses may be misleading due to the increased likelihood of false negative and false positive significance tests with more subgroup analyses, it will be important to report the findings as conditional on the representativeness of the included studies to the true heterogeneous target population. Most importantly, these subgroup analyses aimed to identify potential sources of overall



between-study heterogeneity. They also aimed to possibly describe the relative influence of certain variables on the overall heterogeneity in the effect estimate of aerobic exercise on CPF in the CCS population.

Unfortunately, since only nine studies were included in the review, and a meta-regression is only recommended for meta-analyses with 10 or more studies,<sup>187</sup> a meta-regression was not performed. Therefore, a prediction model for the outcome measure of interest according to any of the investigated subgroup variables was not possible.

#### **b. Sensitivity Analyses**

Sensitivity analyses are conducted in systematic reviews to prove that its findings are not dependent on any potentially arbitrary decisions (i.e., for cut-off, eligibility criteria, or imputation) that are included in the review methodology. This includes substituting alternative decisions for the chosen decisions, and comparing the resulting effect estimate to the original effect estimate. Sensitivity analyses conducted for this review included:

1. Including studies with any overall risk of bias vs. only including studies with low risk of bias;
2. Imputing the average SD vs. imputing the highest SD in cases where SD is missing for the reported or derived change score of a study;
3. Imputing the average SD vs. imputing the lowest SD in cases where SD is missing for the reported or derived change score of a study;
4. Using random-effects meta-analysis vs. fixed-effect meta-analysis;
5. Using the reported SD values (when they are available) vs. deriving all possible SD values using reported p-values and F-values; and

6. Using SD values derived from change score p- and F-values vs. using SD values derived from other p-values or F-values too (“other p-values” refers to p-values or F-values for difference in final values, or repeated measures, between groups).

These sensitivity analyses were assessed using forest plots, similar to how subgroup analyses were assessed (i.e., using the test for subgroup differences in RevMan software, with a significant Chi<sup>2</sup> statistic having a p-value > 0.1). In all sensitivity analyses, a significant Chi<sup>2</sup> statistic indicated a significant difference in the two different decisions tested, and thus, evidence of the possible dependence of the effect estimate on the chosen arbitrary decision.

## Chapter 4: Results

The main purpose of this systematic review and meta-analysis was to attempt to answer the following question: “What is the effect of aerobic exercise on CPF in CCS treated with a known cardiotoxic agent?” The specific objectives were to evaluate whether the effect was influenced by certain potential sources of heterogeneity (i.e., sources of clinical diversity), in this specific population. This chapter includes a detailed description of the search results for this review; the results of the screening process; the characteristics of the included studies; and the results of the statistical analyses of pooled data from the included studies. This chapter was written in a format that conforms to guidelines put forth by the Cochrane Collaboration, as described in the Cochrane Handbook.<sup>187</sup>

### I. Study Selection

The search for, and selection of studies for inclusion in the review was a multi-step process, involving multiple authors, and multiple sources of studies (each source constituting a separate “search strategy”). The specific search strategies, and the steps for selection of studies from the results of each search strategy, including how many authors were involved for each, are outlined in the methods chapter (**Chapter 3, sections II and III**, respectively). The following section summarizes the initial results for each search strategy and how many studies made it past each screening stage, per search strategy. More specifically, each sub-section includes a breakdown of: (1) how many ‘citations’ were initially identified using the respective strategy (e.g., electronic database searching, grey literature searching, etc.); (2) how many unique ‘records’ remained after deduplication of the initial set of citations (if applicable to the specific search strategy);

(3) how many of these records made it through the first screening stage (i.e., screening of title and abstract; if applicable to the specific search strategy); and (4) how many of these records made it through the final screening stage (i.e., screening full-text reports using the inclusion assessment form). The records remaining from each search strategy after these four stages were included in the review.

#### **a. Electronic Database Searching**

Based on the electronic database searches, a total of 3080 citations were found. After deduplication, 2707 PE records remained. The first screening stage excluded a further 2648 records that did not meet the criteria for inclusion. The second screening stage excluded a further 49 records based on a review of the full-text articles. These records were deemed ineligible for a variety of reasons, the main reasons being that some were either exact duplicates or ‘duplicate publications’ (i.e., articles that report on data from the same study, but are not the same publication) of other records that were deemed ineligible, and others were either a list of abstracts or a commentary that was not relevant to the review. Also, two articles (both protocols) had unclear eligibility based on the available information in their full-text articles, and before contacting their authors. These are not counted among the eligible articles yielded from this search strategy. Thus, eight articles were included in the review from this search strategy. Since these included articles included two pairs of duplicate publications, only *six studies* retrieved from the databases were initially included in the review.<sup>199–204</sup> These included studies, and their associated citations/publications, are summarized in **Appendix XII**.

## **b. Grey Literature Searching**

Based on the grey literature searches, just over 6000 citations were found. This number of citations is based on the combined results of the separate search methods used to search all individual grey literature sources, including selected websites, WHO ICTRP, and Google Scholar (**Appendix IX**). The specific methods used to search the websites were categorized as: (1) websites that contained individual PE results (e.g., abstracts and/or reports of studies); (2) websites that contained conference proceedings; and (3) websites that contained neither (**Chapter 3, section II.b**). It should be noted that the citations retrieved from the websites that make up part of the total citations retrieved from grey literature only account for those that were either retrieved directly from the website itself, or from basic Google searches. Meanwhile, the numbers of citations retrieved from the searches within conference proceedings were not recorded, and therefore are not included in the total number of citations yielded from grey literature. Of the grey literature citations initially retrieved, only 16 PE records remained after the first screening stage. All 16 were deemed ineligible in the second screening stage.

It is important to note that not all citations retrieved from each grey literature source were screened due to: (1) time constraints; and (2) the high likelihood that screening of more citations would have yielded no new PE records. For example, only the first 100 citations retrieved from both the American Cancer Society and German Josep Carreras Leukemia Foundation websites via Google advanced search, were screened. Since none of these citations (from either website) were deemed PE, it was decided to discontinue screening the search results from both these websites. Other grey literature sources that had their searches limited in a similar way were: (1) the Google search results for

"American Institute for Cancer Research conference proceedings"; and (2) the Google search results for "exercise Dutch Cancer Society conference". While it is possible that limiting screening in this way actually did preclude the discovery of other PE citations, some of which may have even been included in the review, this was deemed unlikely. A quantitative description of how many records were retrieved from each grey literature search strategy vs. how many records were fully screened is included in **Appendix XIII**.

### **c. Additional Search Strategies**

As detailed in the methods chapter, the authors who were contacted to identify further trials included: (1) the authors of the already included studies; (2) the authors of the studies that met most of the eligibility criteria, but were ultimately excluded; and (3) the authors of studies that a judgement was not possible based on the currently available information. The authors described by (1) and (2), and that replied to an initial e-mail and/or a follow-up e-mail, suggested six possible studies for the review. Some of these studies were deemed ineligible; others had already been identified via a previous search strategy; and the rest were ongoing studies that had not been released or published any data or findings to date. Furthermore, upon contacting the authors of the ongoing studies, all were unwilling to share further data or findings.

By contrast, the authors described by (3) provided information and/or unpublished data for the two studies that had previously been judged as unclear for eligibility (based on the information provided in their protocols).<sup>205,206</sup> This new information and data were used to move both studies through the second screening stage, and effectively confirm eligibility for both. Thus, contacting authors added a *seventh and eighth study* to the

review. These studies, and their associated citations<sup>205,206</sup> are also included in **Appendix XII**.

Based on reference list searching of relevant reviews identified via database searching (n=25 reviews),<sup>77–80,174,181,207–224</sup> and articles associated with eligible studies (i.e., the eight included articles from the database search results + the two protocol articles that were included after contacting authors),<sup>199–206</sup> a total of 105 PE citations were found, most of which were from the review reference lists. After deduplication, 50 PE records remained. The first screening stage excluded a further 46 records, some of which were excluded because they could not be accessed since there was no electronic/digital copy of the record's abstract (n=3). Three of the remaining four records were excluded in the second screening stage, while the fourth (which was a dissertation) was initially judged unclear for eligibility, but after contacting the first author, was confirmed as eligible and was thus included as the *ninth* study in the review.<sup>225</sup>

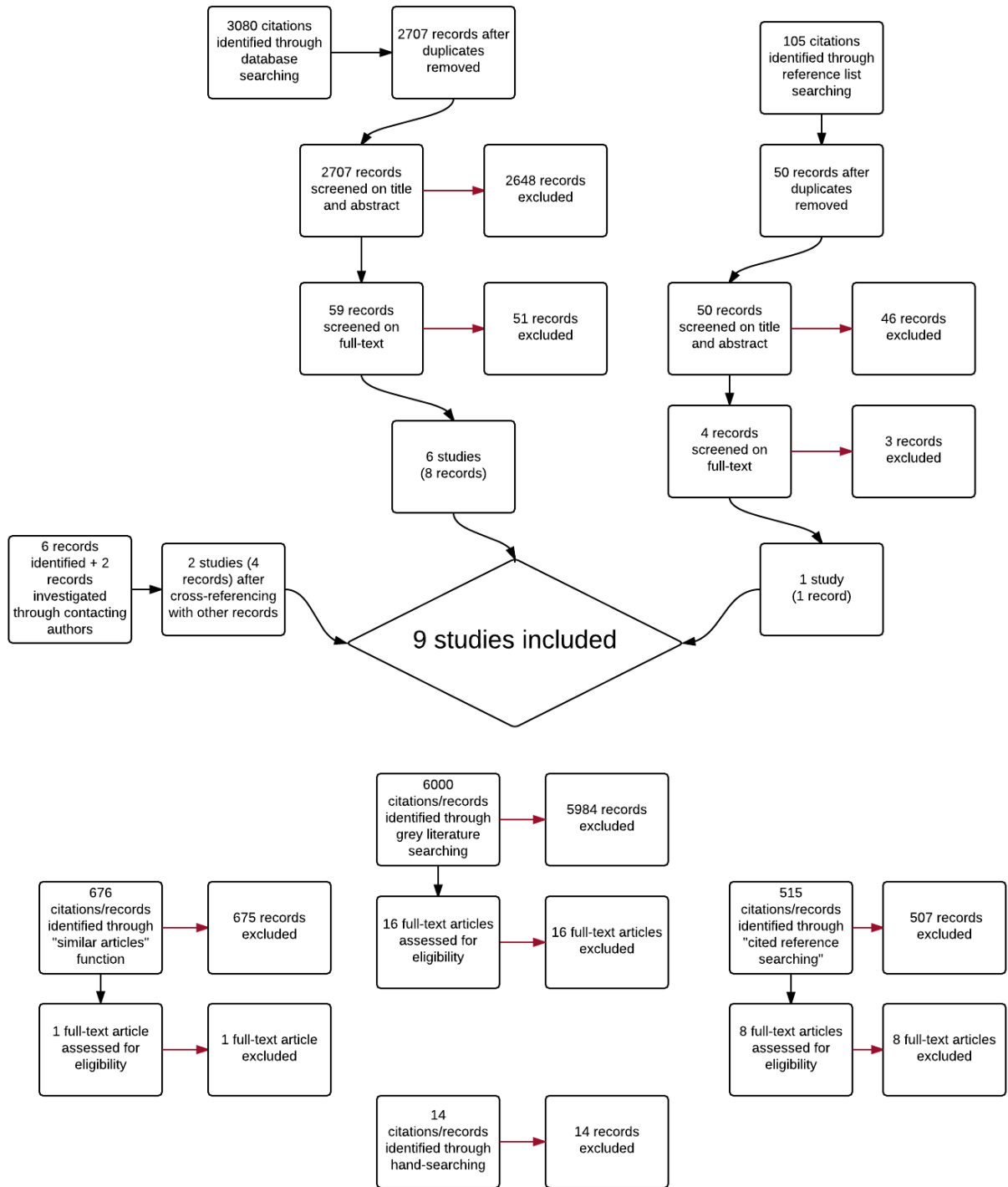
Based on the “similar articles” searches in PubMed, which were done for all of the included studies that were indexed on PubMed, almost 1000 citations were found. Of those, 676 were screened for potential eligibility. The first screening stage excluded 675 records. The one record that remained was excluded in the second screening stage as it did not specifically examine the population of interest for this review. Similar to the grey literature search strategies, it is important to note that not all citations retrieved from each “similar articles” search were screened, due to: (1) time constraints; and/or (2) the high likelihood that screening of more citations would have yielded no new PE records. See **Appendix XIII** for a quantitative description of how many records were retrieved using “similar articles” searching vs. how many records were fully screened.

Based on “cited reference searching” in Web of Science and Google Scholar, which was also done for all eligible studies, 515 citations were found. The first screening stage excluded 507 records. All eight remaining records were excluded in the second screening stage.

Finally, based on hand-searching of all existing issues of the “World Journal of Meta-Analysis”, a total of 14 PE records were found. The first screening stage of these records excluded all of them.

**Figure 1** is a study flow diagram that contains the initial search results for each search strategy, the PE records remaining after the first stage of screening (n=96), the PE records remaining after the second stage of screening (n=13), and the total studies included in the review





**Figure 1:** Study flow diagram (with additional search strategies)

(n=9). All of the described search strategies were initiated in November 2015 (or later) and were completed by April 2016.

## II. Characteristics of Included Studies

The nine studies included in the review met the eligibility criteria for the review. Within the 13 reports associated with the included studies, there were four pairs of duplicate publications. These pairs include the following: Gocha (dissertation)<sup>226</sup> and Marchese et al (published study)<sup>201</sup>; Braam et al (published protocol)<sup>205</sup> and van Dijk-Lokkart et al (published study)<sup>227</sup>; Shore (dissertation)<sup>200</sup> and Shore and Shepard (published study)<sup>228</sup>; and Chiang et al (dissertation, non-English)<sup>225</sup> and Yeh et al (published study)<sup>229</sup>. The remaining four articles and one dissertation were each individually associated with one of the other included studies.<sup>199,202-204,206</sup> For a detailed summary of the characteristics of each included study, refer to each study's respective 'Characteristics of included study' table (**Appendices XIV-XXII**). For a more concise summary of the most salient characteristics of each included study see **Table 2**.

**Table 2:** Table of the major characteristics of included studies

Study ID	Study #	Methods characteristics			Participants characteristics			
		Study design	Length of study	Power calculation? Met/not met?	Mean age	Diagnosis (% ALL)	Treatment (% AC)	Treatment status
<i>Dubnov-Raz 2015</i>	1	CCT	Not reported	No	EX: 11.1; CON: 11.8*	36%	Unclear <sup>§</sup>	100% On
<i>Shore 1998</i>	2	CCT	8 months	No	EX: 14; CON: 13	50%	33%	67% On, 33% Off
<i>Braam 2010</i>	3	RCT	6 years & 5 months	Yes (26 participants per group necessary); met	Both: 12.8	≈45% <sup>#</sup>	≈100%	32% On, 68% Off
<i>Soares-Miranda 2013</i>	4	RCT	3 years	Yes (60 participants total necessary); not met	EX: 10; CON: 12	0% (due to exclusion criterion)	89.9%	100% On
<i>Marchese 2003</i>	5	RCT	Not reported	No	Both: 8.1; EX: 8.6; CON: 7.6	100%	Unclear <sup>§</sup>	100% On
<i>Moyer-Mileur 2009</i>	6	RCT	Not reported	No	EX: 7.2; CON: 5.9	100%	100%	100% On
<i>Tanir 2012</i>	7	RCT	10 months	No	EX: 10.21; CON: 10.72	100%	Unclear <sup>§</sup>	100% Off
<i>Chiang 2007</i>	8	CCT	13 months	No	EX: 11.01; CON: 12.48	100%	Unclear <sup>§</sup>	100% On
<i>Niesen-Vertommen, 1998</i>	9	CCT	Not reported	Yes (8 participants per group necessary); met	EX: 11.8; CON: 10.6	44%	66%	100% Off

ALL = acute lymphoblastic leukemia; AC = anthracycline therapy; \*median instead of mean; <sup>#</sup>In Braam et al., 2014,<sup>230</sup> it was reported that over 60% of participants in the *Braam 2010* study had been diagnosed with a haematological malignancy (based on data available at the time). Given that recent statistics on childhood leukemia in Canada found that ≈75% of leukemia patients are diagnosed with ALL,<sup>231</sup> it was approximated that 45% of participants in *Braam 2010* were ALL survivors. <sup>§</sup>AC was not reported for these studies, but it should not be ruled out.

**Table 2:** Table of the major characteristics of included studies (cont'd)

Study ID	Study #	Interventions Characteristics					Outcomes characteristics		
		S/S vs. H/I	Intensity	Duration	Dose (mins/week)	Volume (total mins)	Additional time points (not baseline & post-test)	Type of exercise test	Age-matched validation of exercise test
<i>Dubnov-Raz 2015</i>	1	S/S	Moderate	6 months	180	4,320	None	Maximal	Yes
<i>Shore 1998</i>	2	S/S	70-85% HR <sub>max</sub> *	3 months	90-120	1,080-1440	None	Maximal	No
<i>Braam 2010</i>	3	S/S	66*-90%# HR <sub>max</sub>	3 months	90+	1,080+	9 months follow-up	Maximal	Yes
<i>Soares-Miranda 2013</i>	4	S/S	60-70% HR <sub>max</sub> *	9-41 weeks	90	810-3,690	2 months follow-up	Maximal	No
<i>Marchese 2003</i>	5	H/I	≈70% HR <sub>max</sub> * <sup>Δ</sup>	4 months	Variab le <sup>Δ</sup>	NC	None	Submax.	Yes
<i>Moyer-Mileur 2009</i>	6	H/I	Moderate-vigorous	12 months	45+	2,160+	6 months (half-way)	Submax.	Yes
<i>Tanir 2012</i>	7	H/I	Not reported	3 months	90	1,080	None	Submax.	Yes
<i>Chiang 2007</i>	8	H/I	40-60% HRR*	6 weeks	30-90	180-540	None	Maximal	No
<i>Niesen-Vertommen, 1998</i>	9	H/I	60*-80%# HR <sub>max</sub>	3 months	75-150	900-1,800	6 weeks (half-way)	Maximal	No

S/S = supervised/standardized; H/I = home-based/individualized; HR<sub>max</sub> = Maximum predicted heart rate; HRR = heart rate reserve; NC = not enough information to calculate; \*Indicates moderate intensity;<sup>232</sup> #Indicates high intensity;<sup>232</sup> <sup>Δ</sup>Specific intensity and dose was not reported for this study. However, it was stated that (1) intensity and dose were variable; (2) they were based on the observation and judgement of a therapist in charge of prescribing exercise and monitoring HR for each participant; and (3) they were based on the Winningham (1991) walking program for people with cancer<sup>233</sup> with modification for the pediatric population.

### a. Methods Characteristics

**Studies 3-7** were RCTs,<sup>201-203,205,206</sup> while **studies 1, 2, 8, and 9** used a quasi-experimental study design, making them CCTs.<sup>199,200,204,225</sup> The length of the studies ranged considerably from 8 months in length (**study 2**)<sup>200</sup> to 6.5 years (**study 3**).<sup>205</sup> The three other studies that reported start and end dates were 13 months (**study 8**),<sup>225</sup> 10 months (**study 7**),<sup>203</sup> and 3 years in length (**study 4**).<sup>206</sup> **Studies 1, 5, 6, and 9** did not report any information on study duration.<sup>199,201,202,204</sup>

The main aim of each of the included studies varied somewhat, but all had a common aim of determining the effect of an aerobic exercise intervention on CPF. A general secondary objective of the included studies was exploring the effects of exercise on other outcomes of interest. These included body composition,<sup>199,202,204</sup> QoL (including ratings of mental and/or psychological health),<sup>199,201,203,204</sup> immune profile,<sup>200,206</sup> muscle strength,<sup>201,202,205</sup> “cancer control”,<sup>206</sup> PA levels,<sup>204,206</sup> range of motion,<sup>201</sup> flexibility,<sup>202</sup> blood parameters,<sup>203</sup> echocardiography results,<sup>204</sup> fatigue,<sup>225</sup> pulmonary function,<sup>204</sup> and anaerobic capacity.<sup>204</sup> Other secondary objectives included examining how exercise affects both CPF and other outcome variables in cancers other than leukemia (**study 1**)<sup>199</sup>; examining how the effects of exercise are modified by morbidity, co-morbidity, and/or subsequent chemotherapy (**study 2**)<sup>200</sup>; examining the short- and long-term effectiveness of the intervention (**study 3**)<sup>205</sup>; assessing feasibility of such an intervention (**studies 6 and 8**)<sup>202,225</sup>; and identifying the independent direct and indirect effects of the disease and/or its treatment in long-term CCS (**study 9**).<sup>204</sup>

Only three studies (**studies 3, 4, and 9**) performed a power calculation for the outcome of CPF.<sup>204-206</sup> A power calculation is used to determine the minimal sample size

necessary to detect a certain effect size with statistical significance ( $p$ -value < 0.05), with a certain amount of power (i.e., the probability of accurately rejecting the null hypothesis; minimum accepted level is 80%).<sup>234</sup> In **studies 3 and 4**, the unit of the detectable difference used in the calculation was percent change in relative VO<sub>2</sub> peak.<sup>205,206</sup> In **study 3**,<sup>205</sup> a target of 26 participants per group was needed to detect a clinically relevant result (i.e., 20% difference in VO<sub>2</sub> peak) with 80% power, and this was attained. The same cannot be said of **study 4**,<sup>206</sup> which did not attain the calculated target sample size of 60 patients in order to detect a clinically relevant improvement in VO<sub>2</sub> peak with 80% power, using an alpha value of 0.008. Meanwhile, **study 9** found that only 8 subjects per group were needed to detect a clinically relevant difference, with 80% power.<sup>204</sup> Although this was attained, based on the recruitment of 18 subjects in total, the study failed to reach its goal of 20 subjects per group, which it had set by doubling its target to include both males and females, and allowing for a 20% attrition rate.<sup>204</sup> None of the other studies performed a power calculation based on relative VO<sub>2</sub> peak or any other outcome variable.

Few studies explicitly employed strategies to address diversity/disadvantage (**Chapter 3, section IV, participant characteristics**) during recruitment. Addressing diversity/disadvantage in recruitment is important to avoid unwanted “non-response bias” in the sample, due to self-selection. Non-response bias is the bias that results when non-respondents differ from respondents, on potentially meaningful criteria, and which may decrease representativeness.<sup>235</sup> One study that did monitor for non-response bias was **study 3**.<sup>205</sup> This study collected information on sociodemographic characteristics (i.e., daily PA levels, general QoL, behavioural problems, disease, and treatment) that could be used to compare respondents to non-respondents. Using this information, two differences between

respondents and non-respondents were found. Specifically, the results showed that: (1) non-respondents rated their fitness level higher compared with respondents; and (2) respondents were more likely to report internalizing behavioural problems than non-respondents. However, there were no differences between respondents and non-respondents for general and medical characteristics.<sup>227</sup> **Study 5** on the other hand, made an attempt to reduce the potential for non-response bias by both individualizing their intervention and making it home-based, which aimed to reduce non-response caused by unfeasible intensity, or a need to travel.<sup>201</sup> Unfortunately, it is unclear if this strategy proved effective, as no measurement of the difference(s) between respondents and non-respondents was ever reported. This may have also been the motive (or part of the motive) behind the individualization and home-implementation of the programs in **studies 6, 7 and 8**,<sup>202,203,225</sup> although this was not explicitly stated, nor was the difference between respondents and non-respondents reported or retrieved for any of these studies.

One other methods-related characteristic of the included studies is the set of measures collected to avoid, or control for, meaningful baseline imbalances between groups. This was best addressed in **study 3**,<sup>205</sup> which did so via stratified and randomized allocation by type of malignancy, pubertal stage, and phase of treatment. Three other studies (two randomized [**studies 5 and 6**],<sup>201,202</sup> one non-randomized [**study 8**]<sup>225</sup>) were also able to prevent significant baseline imbalances on certain participant characteristics (e.g., demographic characteristics) by either stratifying (randomized studies) or matching of groups (non-randomized study) on these characteristics. **Studies 1, 4, 7, and 9** also made attempts to address and control for baseline imbalances,<sup>199,203,204,206</sup> but this was done to varying degrees of effectiveness. For example, **study 4** addressed the issue of baseline

imbalance to some degree (i.e., groups were comparable in gender and age),<sup>206</sup> but visual examination of data received directly from one of the authors showed substantial baseline differences in the proportions of certain cancer diagnoses (Alejandro Lucia Mulas, MD, PhD, e-mail communication, January 2016). A similar situation arose in **studies 1 and 7**.<sup>199,203</sup> Thus, despite best efforts, it is possible that studies that did attempt to control for certain baseline characteristics, still contained groups that differed on other characteristics at baseline (e.g., type of treatment, type of malignancy, phase of treatment, etc.). Although this is not an unlikely finding for the CCS population, considering the low prevalence of childhood cancer, it may still have had an important effect on the outcome of the study. **Study 2** was the only study that did not address baseline imbalances.<sup>200</sup> Consequently, the demographic and baseline VO<sub>2</sub> peak data from this study may suggest at least some baseline imbalance.

#### **b. Participant Characteristics**

Review of the included studies revealed that age range did not vary widely between studies, either between the overall samples, or the individual study groups. The lowest age range was 5.2-7.9 years of age (mean = 6.55), reported in **study 6**,<sup>202</sup> while the highest age range was 13-15 years (mean = 13.5), reported in **study 2**<sup>200</sup> (**Table 2**). By comparison, **studies 1, 3, 4, and 7-9** all had mean (median in one case) ages that were in the range of 10–13 years of age,<sup>199,203–206,225</sup> and only **study 5** was below this range with an age range of 4.3-15.8 years.<sup>201</sup>

Another factor with minimal between-study variation was cancer diagnosis, as over half of the included studies had samples with a majority of participants sharing the same diagnosis: ALL. This is partly attributable to the fact that a substantial proportion of the



included studies (**studies 5-8**) had an explicit inclusion criteria requiring participants to have been diagnosed with ALL.<sup>201-203,225</sup> Four other studies that placed no restriction on what type of diagnosis was eligible for the study either ended up having a majority of ALL survivors in their sample (**studies 1, 2 and 9**),<sup>199,200,204</sup> or had a majority of participants “treated for a haematological malignancy” (**study 3**).<sup>230</sup> It should be noted that **study 2** indicated a “focus” on ALL survivors.<sup>200</sup> Lastly, only **study 4** had an inclusion criterion which rendered ALL survivors ineligible for the study (i.e., “new diagnosis of an extracranial solid tumor”).<sup>206</sup>

Contrary to the aforementioned participant characteristics, there are others which varied more between studies, due to either the variation in the study-specific inclusion/exclusion criteria, or some unintentional variation in the participants recruited per study. One characteristic for which this was the case is treatment received. Although many studies reported that some participants received at least some dose of AC treatment, there is a wide range in the proportion of participants that received AC across studies. **Study 6** reported that 100% of its participants received at least some AC.<sup>202</sup> **Studies 3, 4, and 9** reported that two thirds or more of the sample received at least some AC.<sup>204-206</sup> It should be noted that in **study 9**, the participants in the exercise group that received AC, actually received a higher average dose than the participants in the control group that received AC.<sup>204</sup> While neither group surpassed the average dose of AC generally associated with high-risk of CT (i.e., 300 mg/m<sup>2</sup>),<sup>129,130</sup> the exercise group is at higher risk of cardiotoxic damage, since more patients in this group also received radiation associated with cardiac exposure.<sup>129</sup> For the other studies, it was either reported that fewer than 50% of participants received AC (**study 2**),<sup>200</sup> or there was no specific

mention of AC at all (**studies 1, 5, 7, and 8**).<sup>199,201,203,225</sup> However, since AC is such a common chemotherapy for childhood cancer,<sup>236</sup> and since both the latter groups of studies reported high percentages of other treatments that conceivably could have included AC (i.e., non-specific chemotherapy), or are commonly used in combination with AC (i.e., bone marrow transplant, radiation therapy),<sup>237</sup> AC exposure should not be ruled out for these participants. Importantly, the majority of studies simply stated how many participants received some AC at some point, and provided little to no detail regarding TCD (with the exception of **study 9**),<sup>204</sup> or length of protocol for AC, both of which may therefore be a source of even further between study variability.

Another factor for which between-study variability was high was treatment status. In **studies 1, 4-6, and 8**, all participants were still currently receiving treatment for their cancer when they were completing the exercise intervention.<sup>201,202,206,225</sup> In **studies 5, 6, and 8**, this was due to an inclusion criterion.<sup>201,202,225</sup> In addition, all of the participants in **studies 5 and 8** were receiving maintenance therapy, which is one type of therapy given to some cancer survivors once they have gone into remission (i.e., post-remission therapy).<sup>201,225</sup> In **studies 7 and 9**, it was assumed that the majority of participants were no longer receiving treatment for their cancer, and in both of these cases, this was due to an inclusion criterion.<sup>203,204</sup> For instance, in **study 7**,<sup>203</sup> the inclusion criteria specified that in order for participants to be eligible, they must have received their cancer diagnosis at least 1 year before the study. Similarly, **study 9**<sup>204</sup> specified that the time since completion of treatment for all cancer participants was on average 5.3 years (range = 1-10 years), with only two participants having completed their treatment less than three years prior. Lastly, **studies 2 and 3** did not specify whether or not participants needed to

be on- or off-treatment to be included in the study.<sup>200,201</sup> Specifically, in **study 2**, 67% of the participants were on-treatment, and the remainder had already completed their treatment regimen.<sup>200</sup> It should also be noted that in this study, all of those participants who were off-treatment were in the control group.<sup>200</sup> Meanwhile, in **study 3**, only 32% were on-treatment, and 68% were off-treatment (specifically, ≤12 months off-treatment).<sup>227</sup> In the latter study, the number of participants on- or off-treatment was comparable between groups (intervention group: 30% on, 70% off; control group: 34.2% on, 65.8% off).<sup>227</sup>

### c. Intervention Characteristics

As already mentioned, the common aim across all studies included in this review was to determine the effect of an aerobic exercise intervention on CPF. While **studies 5, 6, 8, and 9** used a home-based, individualized exercise program to explore this effect in CCS,<sup>201,202,204,225</sup> **studies 1-4, and 7** utilized a supervised, standardized program, with mostly set exercise parameters and progressions across participants.<sup>199,200,203,205,206</sup> One source of within-study variation for the studies that used standardized programs was the intensity of exercise. Specifically, three of the studies that used standardized protocols (**studies 2-4**) prescribed intensity based on the pre-training HR<sub>max</sub> of each participant.<sup>200,205,206</sup> Meanwhile, in the other standardized study (**study 1**), intensity of the intervention was simply described as “moderate” without further elaboration as to how this was determined.<sup>199</sup>

Another parameter responsible for some within-study variation in one study was duration of the program, which in **study 4**,<sup>206</sup> was based on the duration of cancer treatment received by each individual participant. It is also important to note that **studies**

**3 and 6** combined aerobic exercise with another non-PA intervention.<sup>202,205</sup> Specifically, the intervention group in **study 3** received a combined physical and psychosocial intervention,<sup>205</sup> while the intervention in **study 6** was a combined exercise and nutrition education program.<sup>202</sup> Also, in **studies 1, 3-7, and 9**, the intervention included some component that aimed to either increase muscular strength or promote muscular development.<sup>199,201–206</sup>

The exact exercise parameters of the interventions (i.e., intervention length, duration of each session, frequency, intensity, and aerobic exercise modality) varied across studies. The longest intervention (**study 6**) was 12 months in duration,<sup>202</sup> and the shortest (**study 8**) was 6 weeks.<sup>225</sup> The most common intervention duration was 12 weeks, which was observed in **studies 2, 3, and 7**.<sup>200,203,205</sup> Types of aerobic activities (i.e., aerobic exercise modality) implemented in the intervention varied widely across studies, and included cycling/cycle-ergometer pedaling, soccer, skating, cross-country skiing, swimming, running, walking, aerobic games, step-dancing to music, jumping rope, ultimate Frisbee, dodgeball, handball, indoor floor hockey, basketball,<sup>200,203,204,206,225</sup> and other activities that promoted aerobic exercise.<sup>202</sup> **Studies 2, 4, and 6-9** reported using either specific aerobic activities or “activities that promoted aerobic exercise”,<sup>200,202–204,206,225</sup> and four of these (**studies 2, 4, 8, and 9**) also prescribed a target HR zone.<sup>200,204,206,225</sup> There was much variation in the other parameters of exercise (i.e., session duration, frequency, and intensity), and these parameters were used to calculate weekly exercise volume, or “dose” of exercise, in hours/week, at a certain intensity.

Levels of supervision/monitoring also differed widely across studies, with more professional or expert supervision generally being used in the studies that implemented a

standardized program (**studies 1, 3 and 4**).<sup>199,205,206</sup> In fact, only one of the studies that used a standardized program (**study 2**) did not have an expert in charge of supervising the intervention.<sup>200</sup> Furthermore, the therapists that supervised the exercise in **study 3** also received personal instructions for administering the exercise protocol, as well as site visits during the intervention to guarantee uniformity between therapists.<sup>205</sup> By contrast, the studies that implemented personalized, home-based programs (**studies 5-9**), showed either minimal or no professional supervision during the interventions.<sup>201-204,225</sup>

#### **d. Outcome Characteristics**

All studies reported an outcome of CPF at both baseline and post-intervention, with **studies 3, 4, 6, and 9** reporting this outcome at additional time points.<sup>202,204-206</sup> Eight out of the nine studies reported that the post-intervention measurement was recorded immediately following completion of the intervention, whereas **study 3** reported that post-intervention CPF was measured at 1-month follow-up.<sup>205</sup> The studies that reported CPF at an additional (third) time point, did so either during the intervention (**studies 6 and 9**),<sup>202,204</sup> or at some time increment following completion of the intervention (**studies 3 and 4**).<sup>205,206</sup> Both mid-intervention measurements were performed at the half-way point,<sup>202,204</sup> whereas the two follow-up measurements were completed at 2 months (**study 3**),<sup>206</sup> and 9 months follow-up (**study 4**).<sup>205</sup>

Other characteristics of the outcomes reported by the included studies are related to the exercise tests used to measure CPF. **Studies 1-4, 8, and 9** used a maximal test,<sup>199,200,204-206,225</sup> while **studies 5-7** used a submaximal test.<sup>201-203</sup> In studies where maximal tests were conducted, subjects were instructed to exercise to their VO<sub>2</sub> peak, and this was always reported in relative terms (i.e., ‘relative VO<sub>2</sub> peak’; ml/kg/min), even

though the specific exercise protocol used to induce VO<sub>2</sub> peak varied across studies. In these same studies, all maximal tests measured oxygen consumption directly using a metabolic cart. In some of these studies, CPF was also reported in terms of other units, including % of age- and sex-predicted relative VO<sub>2</sub> peak (**study 1**),<sup>199</sup> and absolute VO<sub>2</sub> peak (L/min) (**study 2 and 9**).<sup>200,204</sup>

In contrast, studies that used submaximal tests to assess CPF reported their results using a variety of units. While **studies 5 and 7** used the same protocol to determine CPF (i.e., the 9-minute-run-walk test; 9-MRW),<sup>201,203</sup> the results were reported in different units. Specifically, **study 5** reported the result in terms of metres run/walked,<sup>201</sup> while **study 7** reported the results in terms of the number of 30-metre lengths/cycles completed.<sup>203</sup> **Study 6** utilized the Progressive Aerobic Cardiovascular Endurance Run (PACER) or 20-meter shuttle run test,<sup>238</sup> and reported the result in terms of the number of 20-metre sections completed.<sup>202</sup>

While some of the studies used exercise tests that have previously been validated/used in an age-matched population (**studies 1, 3, and 5-7**),<sup>199,201-203,205</sup> others used tests that have not necessarily been used to measure CPF in children previously (**studies 2 and 8**),<sup>200,225</sup> and/or that did not even provide a reference for their development (**studies 4 and 9**).<sup>204,206</sup> Of the six studies that used a maximal test to measure CPF, only **studies 1 and 3** used a test for which previous studies in an age-matched group could be found (i.e., the Godfrey protocol).<sup>199,205</sup> In contrast, all three studies that used a submaximal test (**studies 5-7**) used protocols that have previously been validated in an age-matched population.<sup>201-203</sup>

One other important outcome-specific characteristic of the included studies is pre-training fitness, since this may affect the detected change in CPF. It can be extrapolated from those included studies that reported pre-training fitness using a similar unit (i.e., relative VO<sub>2</sub> peak in **studies 1-4, 8, and 9**) that there is variation across the included studies,<sup>199,200,204–206</sup> although it is unclear if this variation is significant. The lowest pre-training relative VO<sub>2</sub> peak values were observed in **study 8**,<sup>225</sup> with the combined EX and CON groups averaging a relative VO<sub>2</sub> peak of 24.53 ml/kg/min. The highest pre-training relative VO<sub>2</sub> peak values were reported by **study 2**,<sup>200</sup> with the combined EX and CON groups averaging a relative VO<sub>2</sub> peak of 36.25 ml/kg/min, and the average relative VO<sub>2</sub> peak of the exercise group being markedly (but not significantly) higher than that of the control group (38.8 ml/kg/min vs. 33.7 ml/kg/min, respectively).

As already mentioned earlier, many secondary outcomes were also reported in the studies included in this review. Unfortunately, further details on the secondary outcomes reported by the included studies are outside the scope of this review.

### III. Risk of Bias within Studies

The judgements for each risk of bias domain (**Chapter 3, section IV.a**) for each study and the support for each judgement made, are included in the risk of bias sections of the ‘Characteristics of included study’ tables; there is a separate table for each included study (**Appendices XIV-XXII**). In brief, several important points can be made about the risk of bias judgements for the nine included studies. One is that the study with the lowest risk of bias judgement (**study 5**) still had an unclear judgement for four out of the six risk of bias domains.<sup>201</sup> Also, **studies 1-4 and 7-9** had a high risk of bias judgement for at

least one of the domains,<sup>199,200,203–206,225</sup> with **study 8** having high risk of bias for two items,<sup>225</sup> and **studies 1 and 9** having high risk of bias for three items.<sup>199,204</sup>

Assuming that an unclear risk of bias can be approximated as a high risk of bias, which is consistent with Cochrane guidelines,<sup>239</sup> then the domain with the lowest overall risk of bias (according to all domain-specific risk of bias judgements from all studies combined) is ‘Incomplete Outcome Data’. Meanwhile, the domains with the highest risk of bias are ‘Allocation concealment’ and ‘Other Sources of Bias’.

When the available report(s) did not contain enough (or any) information on one or more of the risk of bias domains, such as was the case in **study 8**<sup>225</sup> for the sequence generation; in **study 1**<sup>199</sup> for selective outcome reporting; and in **study 2**<sup>200</sup> for blinding of outcome assessors, the author(s) were contacted for additional information. In **studies 2 and 8**, additional information was made available by the author(s), and a risk of bias judgement was made accordingly.<sup>200,225</sup>

Furthermore, combining of the individual domain judgements in order to yield overall risk of bias judgements for each study according to the stratification system outlined in the methods chapter (**Chapter 3, section V.a**), resulted in **studies 2-5, and 7** being judged at overall unclear risk of bias,<sup>200,201,203,205,206</sup> and **studies 1, 6, 8, and 9** being judged at overall high risk of bias.<sup>199,202,204,225</sup> Based on the stratification system, no studies were judged at overall low risk of bias.

#### IV. Results of Individual Studies and Synthesis of Results

Some of the CPF results reported by individual studies (e.g., baseline/pre-training values, post-intervention values, change scores), in the original units they were reported,



are summarized in **Table 3**. As already stated, the use of both maximal and submaximal tests by the included studies, and the variation in the reporting of the results of the submaximal tests used, resulted in the outcome of CPF being reported in a total of four different units across the included studies. Therefore, the change score from each study needed to be standardized to % change score (**Chapter 3, equation 3.1** or **3.2**) before calculating individual MD values (i.e., %MD) (**Chapter 3, equation 3.3**). Using these %MD values, the pooled effect estimate for all studies (i.e., %MD<sub>pooled</sub>) was calculated (**Chapter 3, equation 3.4**). The range of % change scores for the control groups of all studies, as well as the %MD<sub>pooled</sub> value for all studies combined, are included in **Table 4**. The range of change scores (un-standardized) for the control groups of the maximal test studies, as well as the pooled effect estimate for all maximal test studies (calculated using un-standardized MD values), are also included in **Table 4**.

**Table 3:** Individual study results for CPF

Study #	Group	Mean baseline CPF	Mean post-intervention CPF	Change score <sup>Δ</sup>
1	EX	32.1 mL/kg/min <sup>s</sup>	37 mL/kg/min <sup>s</sup>	+3.58 mL/kg/min
	CON	31 mL/kg/min <sup>s</sup>	34 mL/kg/min <sup>s</sup>	+1.87 mL/kg/min
2	EX	33.7 mL/kg/min	35.7 mL/kg/min	+2 mL/kg/min
	CON	38.8 mL/kg/min	36.3 mL/kg/min	-2.5 mL/kg/min
3	EX	30.1 mL/kg/min	31.2 mL/kg/min	+1.1 mL/kg/min
	CON	31.4 mL/kg/min	33 mL/kg/min	+1.6 mL/kg/min
4	EX	25.2 mL/kg/min	25.2 mL/kg/min	0 mL/kg/min
	CON	24.2 mL/kg/min	22.5 mL/kg/min	-1.7 mL/kg/min
5	EX	3267.6 m*	3647.2 m*	+379.6 m
	CON	3323.3 m*	3304.5 m*	-18.8 m
6	EX	8 x 20-m <sup>#</sup>	14.64 x 20-m <sup>#</sup>	+6.64 x 20-m
	CON	7.100 x 20-m <sup>#</sup>	14.484 x 20-m <sup>#</sup>	+7.384 x 20-m
7	EX	27.05 x 30-m*	35.89 x 30-m*	+ 8.84 x 30-m
	CON	26.27 x 30-m*	26.76 x 30-m*	+0.49 x 30-m
8	EX	24.57 mL/kg/min	27.03 mL/kg/min	+ 2.46 mL/kg/min
	CON	24.49 mL/kg/min	25.73 mL/kg/min	+1.24 mL/kg/min
9	EX	28 mL/kg/min	31.1 mL/kg/min	+ 3.1 mL/kg/min
	CON	31.7 mL/kg/min	31.6 mL/kg/min	-0.1 mL/kg/min

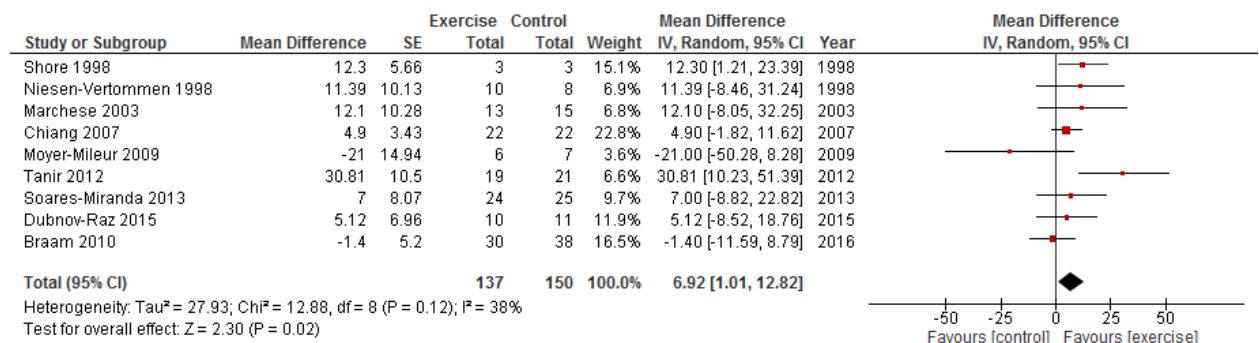
<sup>Δ</sup>Positive (+) indicates an increase in CPF, and negative (-) indicated a decrease in CPF; <sup>s</sup>These values are median values NOT mean values, and were not used in the calculation of change score; \*These are results from the submaximal 9-minute run walk (9-MRW) test. <sup>#</sup>These are results from the submaximal Progressive Aerobic Cardiovascular Endurance Run (PACER).

**Table 4:** Summary of findings table

<b>Aerobic exercise training compared with standard care for childhood cancer survivors during and after cancer treatment</b>				
<b>Patient or population:</b> childhood cancer survivors				
<b>Settings:</b> hospital, community centre, and home				
<b>Intervention:</b> aerobic exercise program				
<b>Comparison:</b> standard care				
<b>Outcomes</b>	<b>Illustrative comparative risks*</b>		<b>No of Participants (studies)</b>	<b>Quality of the evidence (GRADE)</b>
	<b>Assumed risk</b>	<b>Corresponding risk</b>		
	<b>Control group change score (SD)</b>	<b>Exercise group MD (95% CI)</b>		
<b>CRF (% change score &amp; %MD<sub>pooled</sub>)</b> Various scales transformed to % change score Follow-up: N/A	The mean CRF change score ranged across control groups from <b>-7 (28.72) %</b> to <b>104 (28.53) %</b>	The mean CRF change score in the exercise groups was <b>6.92% higher</b> (1.01% higher to 12.82% higher)	287 (9 studies)	⊕⊕⊕⊖ <b>low</b>
<b>VO<sub>2</sub> peak (absolute change score &amp; MD<sub>pooled</sub>)</b> Various maximal tests yielding mL/kg/min Follow-up: N/A	The mean VO <sub>2</sub> peak change score ranged across control groups from <b>-2.5 (1.6) ml/kg/min</b> to <b>1.87 (5.23) ml/kg/min</b>	The mean VO <sub>2</sub> peak change score in the exercise groups was <b>1.39 ml/kg/min higher</b> (0.05 higher to 2.73 higher)	206 participants (6 studies)	⊕⊕⊕⊖ <b>low</b>
<p>*The basis for the <b>assumed risk</b> (e.g. the mean control group change score across studies) is provided in footnotes. The <b>corresponding risk</b> (and its 95% confidence interval) is based on the assumed risk in the control group and the <b>relative effect</b> of the intervention (and its 95% CI).</p> <p><b>CI:</b> Confidence interval; <b>CRF:</b> Cardiorespiratory Fitness; <b>VO<sub>2</sub> peak:</b> outcome of an exercise test that does not reach a true VO<sub>2</sub> max, but does meet at least one of a number of criteria (i.e., 1. maximum heart rate within ± 10 beats of the age-predicted maximum (i.e., 220 – age); 2. a respiratory exchange ratio greater than 1.10; 3. a blood lactate value greater than 8 mmol/L; and/or 4. volitional exhaustion)</p>				
<p>GRADE Working Group grades of evidence<sup>195</sup></p> <p><b>High quality:</b> Further research is very unlikely to change our confidence in the estimate of effect.</p> <p><b>Moderate quality:</b> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p><b>Low quality:</b> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p><b>Very low quality:</b> We are very uncertain about the estimate.</p>				

It should be noted that for **study 1**,<sup>199</sup> the conversion from raw data to % change score values was completed by using both the absolute change scores (which were provided directly by the author) and the median baseline CPF values (which were reported in the study report), for each group.<sup>199</sup> These % change scores were then used to calculate %MD, which was consequently incorporated into %MD<sub>pooled</sub>. This is important to note as the use of median baseline values instead of mean baseline values for the calculation of % change scores may introduce some bias into %MD<sub>pooled</sub>, since the median is not an accurate estimation of mean when sample size is small,<sup>240,241</sup> which it was in this study.

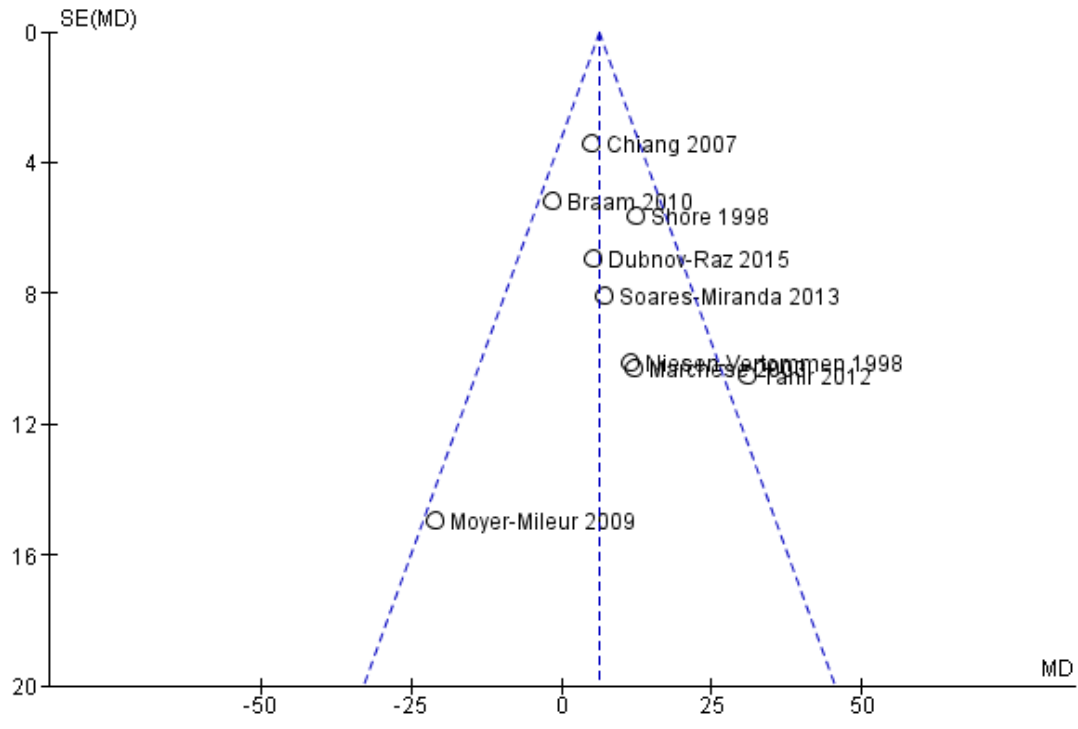
The first main random-effects meta-analysis conducted for this review showed that the effect of an aerobic exercise intervention on CPF, using the standardized unit of %MD, was statistically significant (%MD<sub>pooled</sub> 6.92; 95% CI 1.01 to 12.82; p-value = 0.02). **Figure 2**, which is the forest plot for this meta-analysis, shows the %MD<sub>pooled</sub> and its significance level, as well as the inverse-variance weight of each study (in the column titled “Weight”). The weight of each study is also reflected by the size of the square indicating the point estimate for that study.



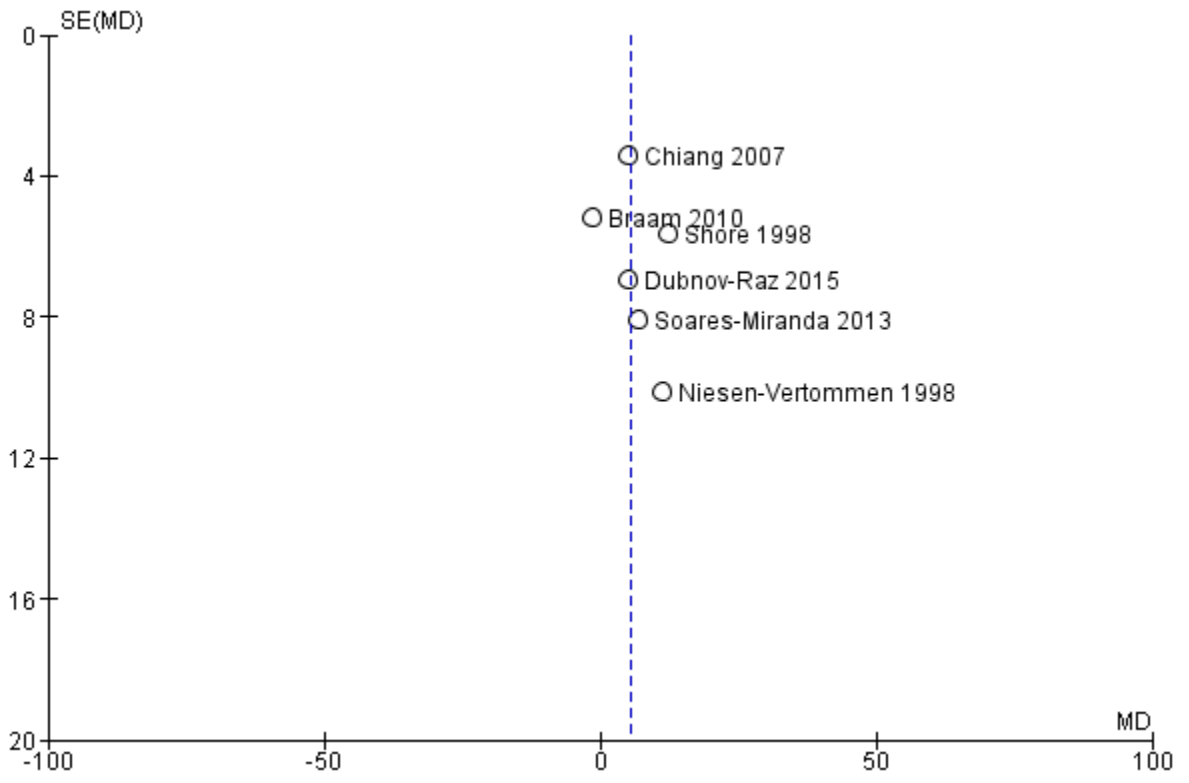
**Figure 2:** Forest plot for random-effects meta-analysis of all studies (CPF; %MD) and percentage of variation that can be attributed to true clinical heterogeneity (I<sup>2</sup>)

As stated in the methods chapter (**Chapter 3, section IV.c**), the *a priori* reason for choosing random-effects meta-analysis was that it was suspected that the included studies represented estimates from several distributions of effects, and not estimates from a distribution of a single effect. Moreover, this choice was supported by the findings of the funnel plots and quantitative analyses (i.e., linear regression analyses) for potential small-studies effects, displayed in **Figures 3-6**, respectively. Specifically, both sets of figures indicated that there was no small-studies effects across the included studies, based on the lack of asymmetry (funnel plots) and the positive y-intercepts (linear regression analyses). Therefore, it was assumed that the random-effects model did not increase the risk of exacerbating the biased results of small studies.

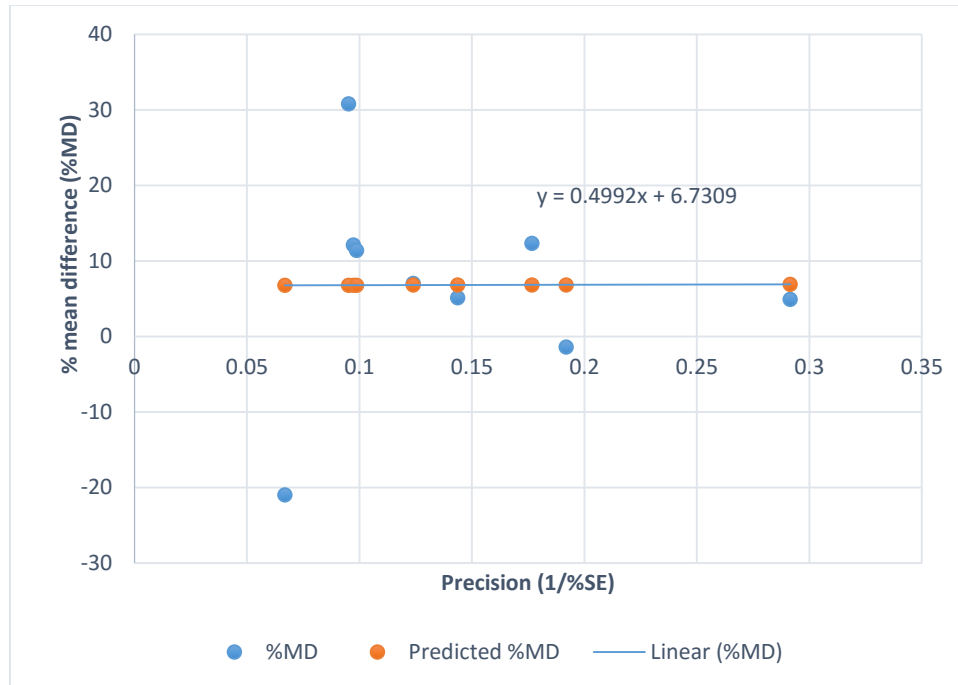
**Figure 2** shows that the two largest weights are associated with the effect estimates from **studies 3 and 8**,<sup>205,225</sup> which have the first and third largest sample sizes, respectively. This was expected, based on the law of large numbers. It should also be noted that the weights of the studies that used a submaximal test (**studies 5-7**)<sup>201-203</sup> were all lower than the weights of the studies that used a maximal test (**studies 1-4, 8, and 9**).<sup>199,200,204-206,225</sup> **Figure 2** also displays the percentage of variation that can be attributed to true clinical heterogeneity (i.e., the  $I^2$  value), and this amount can be categorized as less than substantial (i.e.,  $I^2$  for included studies = 38%; threshold of  $I^2$  for substantial heterogeneity is  $\geq 50\%$ ).<sup>187</sup>



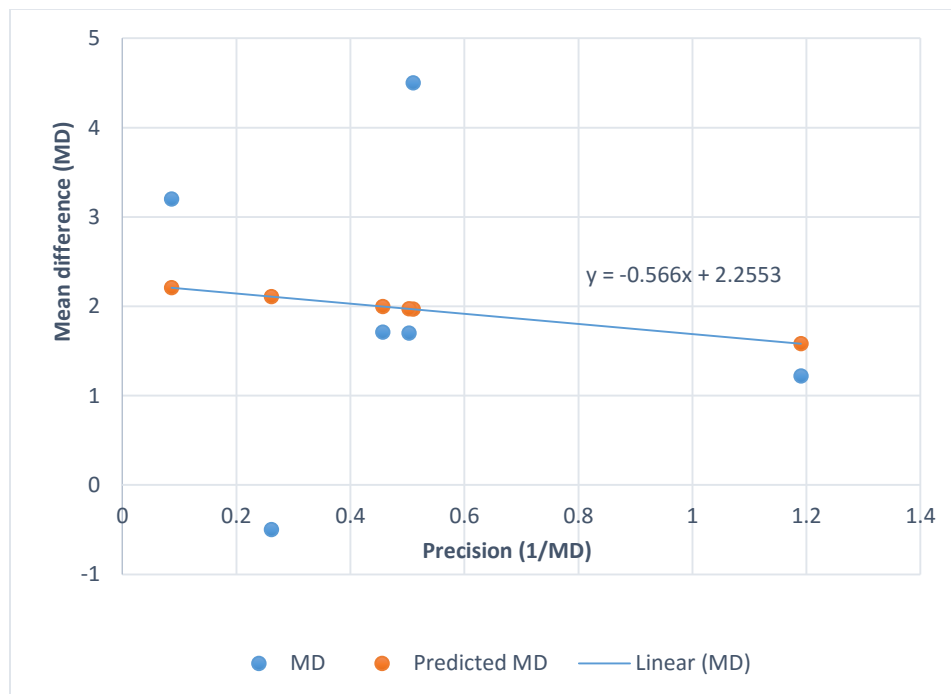
**Figure 3:** Funnel plot of all studies; standard error vs. % mean difference



**Figure 4:** Funnel plot of maximal test studies; standard error vs. % mean difference

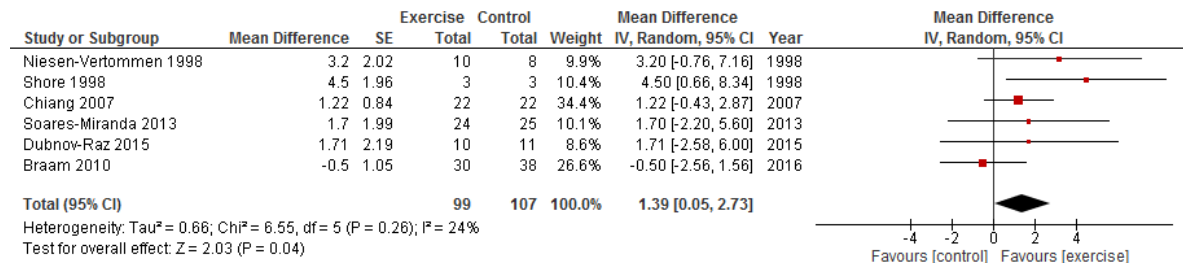


**Figure 5:** Linear regression analysis of all studies. The purpose of this analysis was to quantitatively explore the presence of small-study effects within all included studies.



**Figure 6:** Linear regression analysis of maximal test studies. The purpose of this analysis was to quantitatively explore the presence of small-study effects within the included maximal test studies.

The second main random-effects meta-analysis showed that the effect of an aerobic exercise intervention on relative VO<sub>2</sub> peak was statistically significant (MD 1.39; 95% CI 0.05 to 2.73; p-value = 0.04). As displayed in **Figure 7**, the largest weight is associated with the effect estimate from **study 8**,<sup>225</sup> and the next closest weight (over 50% lower than the former) is associated with the effect estimate from **study 2**.<sup>200</sup> Although the latter study actually has the smallest sample size, it is unlikely that this was a risk for overestimating the overall effect size, because of its relatively low weight when compared to the most heavily weighted effect estimate (10.4% versus 34.4%). Similar to the meta-analysis of all studies, the meta-analysis for these six studies indicated non-substantial heterogeneity across studies ( $I^2 = 24\%$ ). However, in both cases, this does not necessarily mean that there was no clinical heterogeneity; only that it was not discernible from variation due to sampling error, given this specific set of studies and effect estimates.<sup>187</sup>



**Figure 7:** Forest plot for random-effects meta-analysis of maximal test studies: CPF (ml/kg/min)

## V. Subgroup Analyses Results

Many more subgroup analyses were planned *a priori* than were ultimately possible given the number of studies that met the inclusion criteria and the level of detail reported

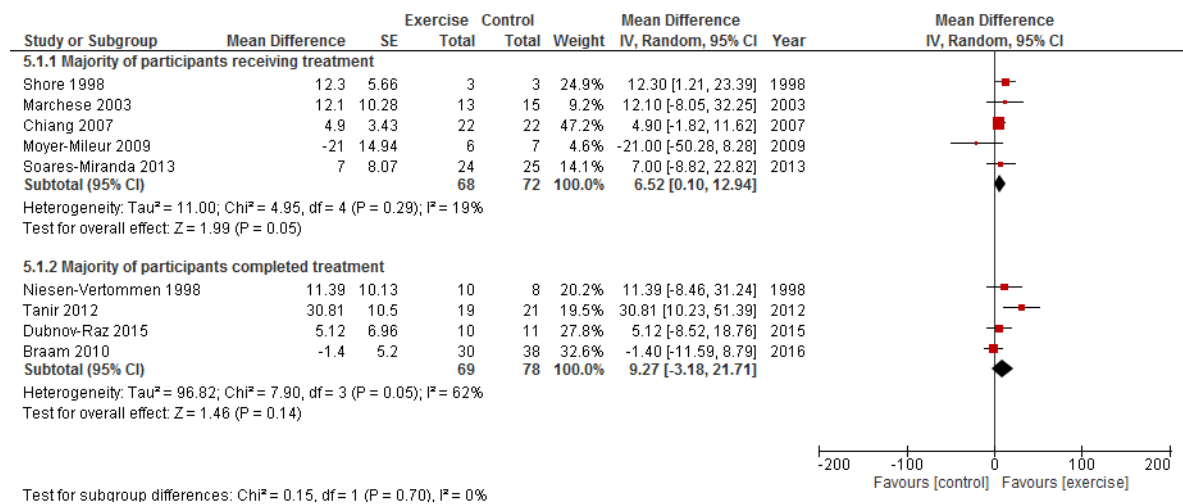


or retrieved for these studies. The *a priori* subgroup analyses that were not completed included those for the following potential sources of heterogeneity: (1) all primary exercise parameters (except for intervention length); (2) reported adherence levels to the exercise program (including adherence levels to specific parameters); (3) levels of aerobic exercise prescription relative to the POEM recommendations for CCS;<sup>69</sup> (4) baseline values of both CPF and exercise; (5) duration since initial cancer diagnosis; (6) follow-up after exercise intervention; (7) age; (8) primary cancer diagnosis; and (9) primary cancer treatment type(s).

The two *a priori* subgroup analyses that were conducted were defined as: (1) majority of participants receiving treatment versus majority of participants completed treatment (hereinafter the treatment status subgroup analysis); and (2) intervention length  $\leq 3$  months versus intervention length  $> 3$  months (hereinafter the intervention length subgroup analysis). As previously mentioned, there was no pre-determined cut-off for the subgroups in the intervention length subgroup analysis. Following extraction of intervention characteristics from all of the included studies, it was determined that studies were concentrated about an intervention length of 3 months, and therefore this length was chosen as the cut-off out of practicality. Ideally, the moderating effect of intervention length would have been examined across more subgroups, however, given the dearth of studies, and the concentration of studies about an intervention length of 3 months, this was the only feasible way to explore this potential source of heterogeneity.

One of the results of the treatment status subgroup analysis, as shown in **Figure 8**, was that the “completed treatment” subgroup had a greater pooled effect estimate (%MD = 9.27, 95% CI -3.18 to 21.71, p-value = 0.14) than the “during treatment” subgroup

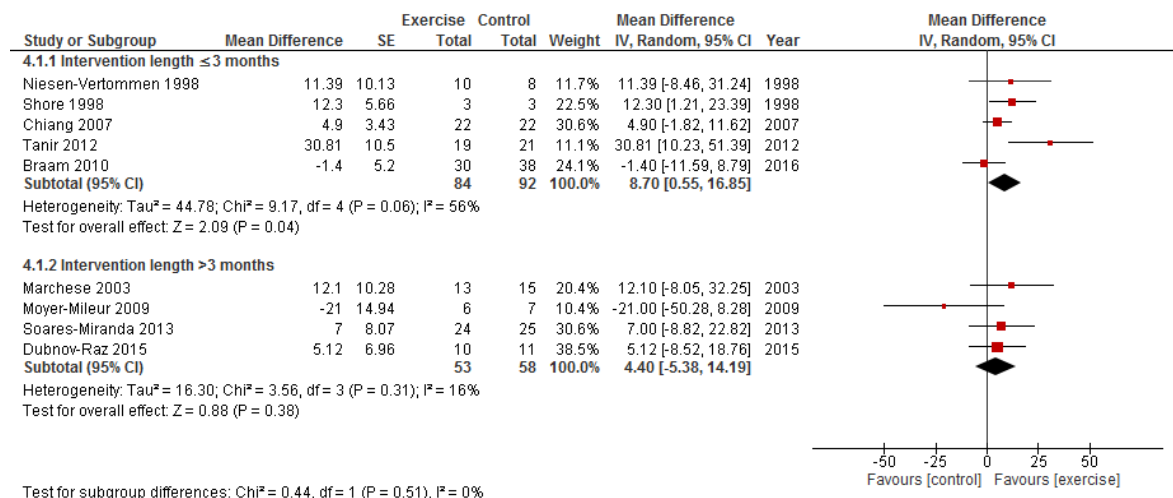
(%MD = 6.52, 95% CI 0.10 to 12.94, p-value = 0.05). However, the subgroups' effect estimates were not significantly different from one another (according to both their 95% CI's and the test for subgroup differences), nor from the overall pooled effect estimate (when comparing their 95% CI's to the 95% CI for the overall effect estimate). It should also be noted that the effect estimate from the 'completed treatment' subgroup lacked significance (p-value = 0.25), while the effect estimate from the 'during treatment' subgroup was nearing significance (p-value = 0.05). Another result of the analysis was that the heterogeneity in the 'completed treatment' subgroup ( $I^2 = 62\%$ ) was greater than both the heterogeneity of the 'during treatment' group ( $I^2 = 19\%$ ), and the overall heterogeneity across all studies ( $I^2 = 38\%$ ).



**Figure 8:** Forest plot for subgroup analysis of majority of participants receiving treatment versus majority of participants completed treatment

One of the results of the intervention length subgroup analysis, as highlighted in **Figure 9**, was that the “ $\leq 3$  months” subgroup actually had a slightly greater pooled effect estimate (%MD = 8.70, 95% CI 0.55 to 16.85, p-value = 0.04) than the “ $> 3$  months” subgroup (%MD = 4.40, 95% CI -5.38 to 14.19, p-value = 0.38). Furthermore, the effect

estimate of the '>3 months' subgroup did not show a significant difference from the null hypothesis (i.e., no effect of an exercise intervention shown), while the '≤3 months' subgroup did (p-value = 0.04). However, the subgroups' effect estimates were not significantly different from one another, nor from the overall pooled effect estimate (again, based on 95% CI's and the test for subgroup differences). In addition, the heterogeneity in the '≤3 months' subgroup was substantial ( $I^2 = 56\%$ ), not to mention greater than the heterogeneity in the overall sample ( $I^2 = 38\%$ ).



**Figure 9:** Forest plot for subgroup analysis of intervention length ≤3 months versus intervention length >3 months

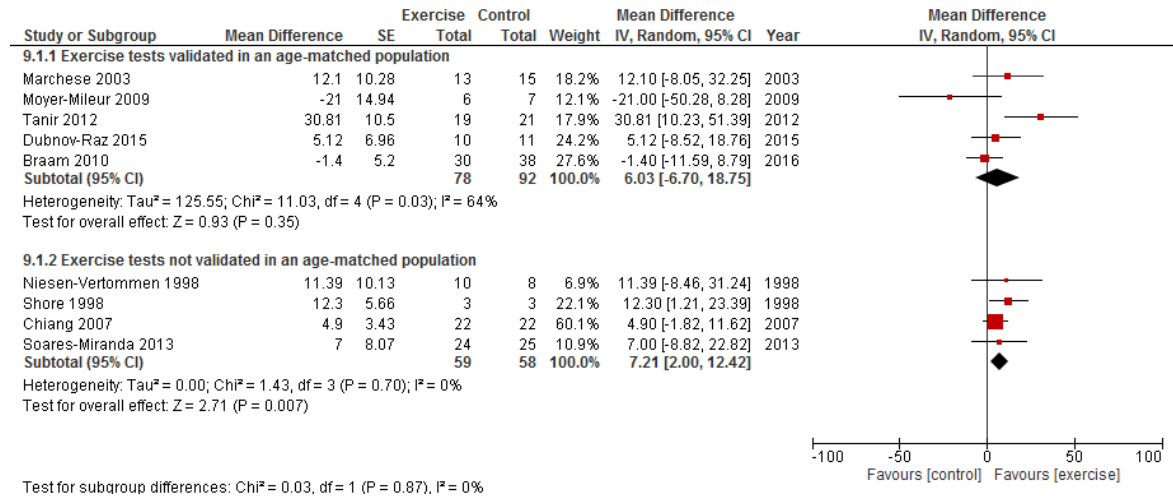
It may be tempting to combine the results of these two *a priori* subgroup analyses, and extrapolate that the common studies from the subgroups with high  $I^2$  values are also the studies that are causing the majority of heterogeneity in the main meta-analyses. However, since each subgroup is comprised of a different combination of studies, there are different proportions of information in each new subgroup, due to the varied weights of the individual studies. Therefore, the subgroups themselves have varying abilities to estimate the true effect of the intervention. For example, the 'completed treatment'

subgroup accounts for 41.9% of the total data from the included studies (according to the combined weights of the studies in this subgroup), whereas the ‘≤3 months’ subgroup accounts for 68% of the total data. These values can be observed in **Figures 8 and 9**, respectively. Thus, subgroup analyses were not used to extrapolate which specific studies are accounting for overall heterogeneity, as it may be misleading to base the source of overall heterogeneity on the findings of a few, variably weighted, subgroup analyses.<sup>187</sup>

Two additional subgroup analyses were completed that were not specified *a priori*. These included maximal test studies versus submaximal test studies (hereinafter the exercise test subgroup analysis), and exercise tests validated/used in an age-matched population versus exercise tests not validated/used in an age-matched population (hereinafter the validation subgroup analysis). The reason these “*post hoc*” subgroup analyses were conducted was that it became apparent that they could be conducted, given the perceived variability across studies on these factors, and the fact that an approximately equal number of the included studies could be allocated to each subgroup for the analysis.

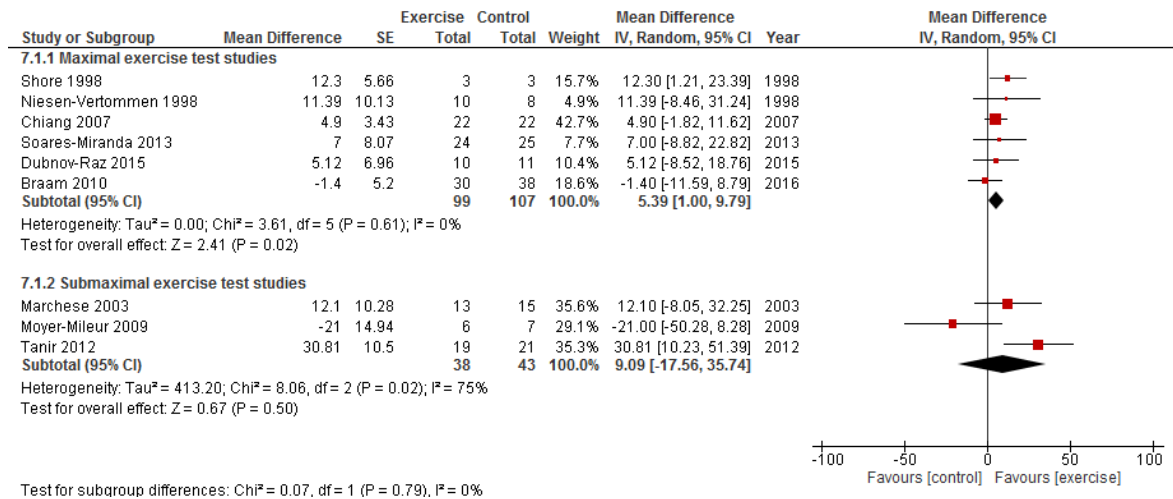
The validation subgroup analysis, displayed in **Figure 10**, showed that the “validated” subgroup had a lower effect estimate (%MD = 6.03, 95% CI -6.70 to 18.75, p-value = 0.35) than the “non-validated” subgroup (%MD = 7.21, 95% CI 2.00 to 12.42, p-value = 0.007). However, the subgroups’ effect estimates were not significantly different from one another, nor from the overall pooled effect estimate. In addition, the effect estimate of the ‘validated’ subgroup lacked significance (p-value = 0.35), and was also substantially heterogeneous ( $I^2 = 64\%$ ), while the ‘non-validated’ subgroup

demonstrated negligible heterogeneity ( $I^2 = 0\%$ ), and had a significant difference from the null hypothesis (p-value = 0.007).



**Figure 10:** Forest plot for subgroup analysis of exercise tests validated in an age-matched population versus exercise tests not validated in an age-matched population

The results of the exercise test subgroup analysis showed a similarly large difference between the subgroups’ effect estimates to that of the intervention length subgroup analysis (%MD = 5.39 for maximal test studies vs. %MD = 9.09 for submaximal test studies) as demonstrated in **Figure 11**. Unfortunately, due primarily to the very large 95% CI of the “submaximal test” subgroup (95% CI -17.56 to 35.74), there is the least support for a difference between the two subgroups’ effect estimates, or of either subgroup effect estimate from the overall pooled effect estimate, based on this subgroup analysis.



**Figure 11:** Forest plot for subgroup analysis of maximal test studies versus submaximal test studies

## VI. Reporting/Publication Bias Results

As previously mentioned, the results of both the funnel plots (**Figures 3 and 4**) and both the linear regression analyses (**Figures 5 and 6**) indicated that there was no small-studies effects for all studies combined (y-intercept = 6.73, 90% CI -15.6 to 29.1, p-value = 0.59), or for the subset of studies that employed maximal tests (y-intercept = 2.26, 90% CI -0.68 to 5.19, p-value = 0.17).

Originally, a sensitivity analysis for examining the effect of including versus excluding studies that display either a ‘high’ or ‘unclear’ risk of bias for selective outcome reporting was planned (i.e., all studies included in the review versus studies that had ‘low’ risk of bias for selective outcome reporting) since it was thought that including these studies may lead to “selective reporting bias”. Unfortunately, this sensitivity analyses was not possible since it was discovered that seven of the nine included studies were judged at ‘unclear’ risk for this domain of bias, and only two studies at ‘low’ risk

for this domain.<sup>202</sup> Therefore, the only findings for whether any reporting bias exists within the sample of included studies are the funnel plots and linear regression analyses previously mentioned.

## VII. Sensitivity Analyses Results

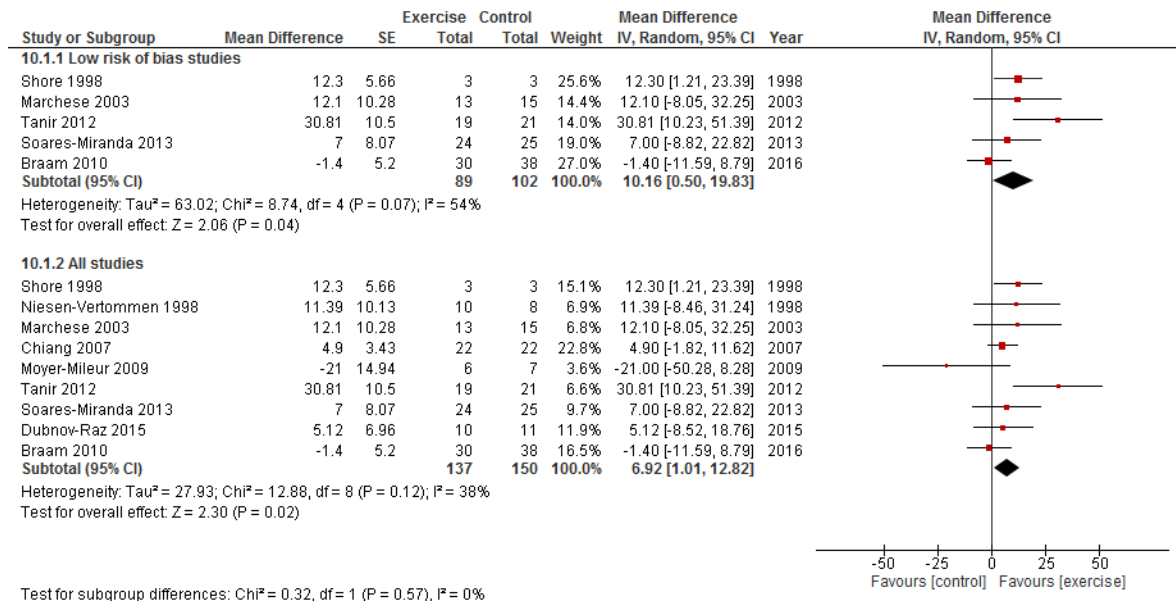
Of the eight sensitivity analyses that were originally planned, only four were conducted. The sensitivity analyses that were not conducted were those based on potentially arbitrary decisions for inclusion or analysis, related to the following factors: (1) blinding of the outcome assessors; (2) selective outcome reporting; (3) change scores versus final scores; and (4) characteristics of cardiotoxic treatment received.

The four *a priori* sensitivity analyses that were conducted can be more specifically described as including studies with any overall risk of bias versus only including studies with low risk of bias (hereinafter risk of bias sensitivity analysis); using fixed-effect meta-analysis model versus random-effects meta-analysis model (hereinafter model sensitivity analysis); and two sensitivity analysis based on imputing different SDs (for the two studies [**studies 3 and 9**] that needed to impute SD values).<sup>204,205</sup> The two SD-related sensitivity analyses can be more specifically described as a sensitivity analysis of imputing the highest SD instead of mean SD (hereinafter the highest SD sensitivity analysis); and a sensitivity analysis of imputing the lowest SD instead of mean SD (hereinafter the lowest SD sensitivity analysis). It should be noted that the “low risk of bias” subgroup used in the risk of bias sensitivity analysis needed to be modified to including those studies with an unclear overall risk of bias instead of those with a low overall risk of bias, since no studies were judged as having the latter.

Furthermore, two other *post hoc* sensitivity analyses were conducted in order to further ensure that any arbitrary decisions made throughout the process of conducting the actual review, did not inadvertently influence its results. Specifically, these are the sensitivity analyses of deriving all possible SD values using reported p-values or F-values versus using the reported SD values (hereinafter p-value versus reported SD sensitivity analysis); and only using SD values derived from change score p- & F-values versus using SD values derived from other p-values too (hereinafter change score p-value sensitivity analysis). “Other p-values” in this instance refers to p-values or F-values related to the difference in final values, or repeated measures.

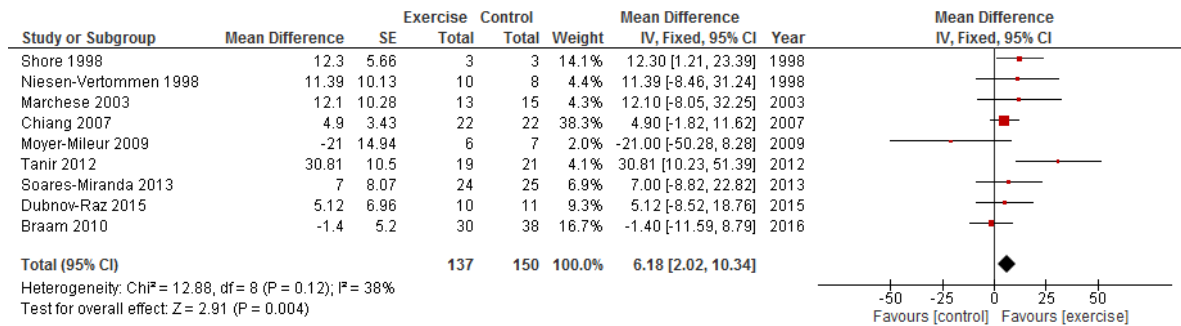
The risk of bias sensitivity analysis (**Figure 12**) showed that the subgroup of studies with unclear risk of bias had a somewhat greater pooled effect estimate (%MD = 10.16 versus %MD = 6.92) than all studies combined (i.e., the studies with any overall risk of bias), that was also statistically significant (p-value = 0.04). Unfortunately, only including those studies with an unclear risk of bias in the meta-analysis was also associated with higher between-study heterogeneity ( $I^2 = 54\%$ ) relative to the heterogeneity for all studies combined ( $I^2 = 38\%$ ). Furthermore, the pooled effect estimate for the unclear risk of bias subgroup is not significantly different from the pooled effect estimate of all studies, according to the 95% CI's. This sensitivity analysis shows that although the unclear risk of bias subgroup studies showed a higher effect estimate, it was at the cost of increased heterogeneity.





**Figure 12:** Forest plot for sensitivity analysis of studies with low risk of bias versus all studies

The model sensitivity analysis was conducted differently, and provided slightly different information. Specifically, it did not include a comparison of information for two different groups of studies, it simply compared the significance and the heterogeneity of the overall effect estimate using a fixed-effect model (**Figure 13**), to the same values when using the chosen model (i.e., random-effects model). One of the results of this sensitivity analysis is that the overall effect estimate using the random-effects model (%MD = 6.92) is slightly larger than the overall effect estimate yielded using the fixed-effect model (%MD = 6.18). This sensitivity analysis also showed that the “random-effects” effect estimate had a larger 95% CI than the “fixed-effect” effect estimate (1.01 to 12.82 versus 2.02 to 10.34, respectively), as displayed in **Figures 2** and **13**. This sensitivity analysis showed that there was significant heterogeneity in the studies regardless of the model used – if the heterogeneity was not significant, the effect estimate would have been the same regardless of the model used.



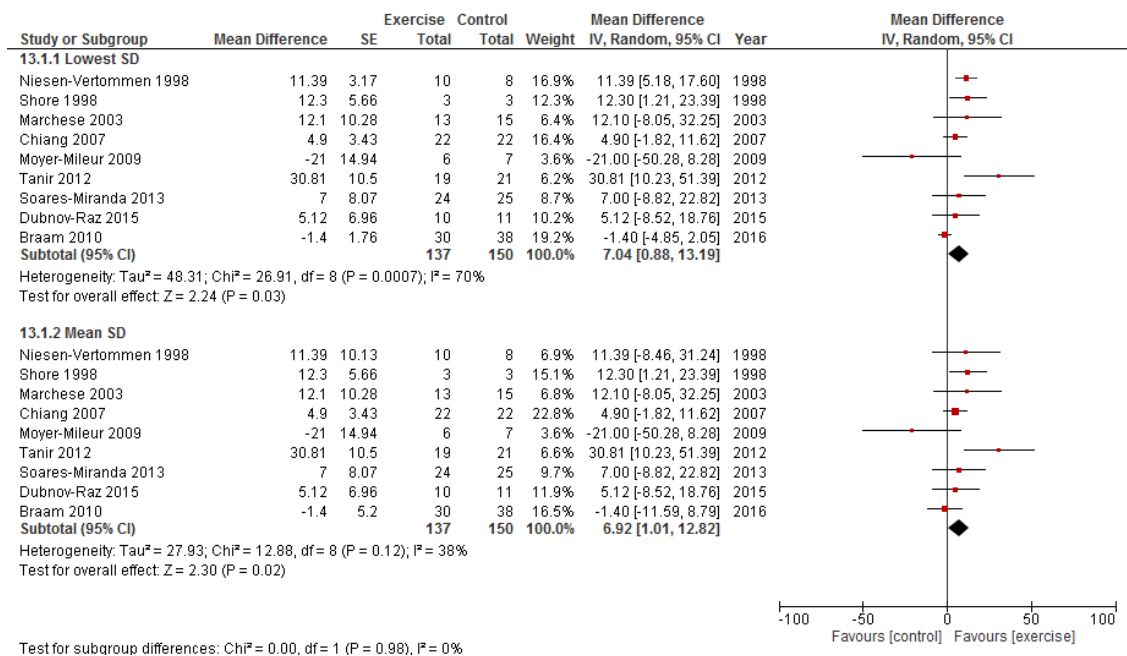
**Figure 13:** Forest plot for fixed-effect meta-analysis of all studies: CPF (%MD)

The result of the lowest SD sensitivity analysis (**Figure 14**) was that the effect estimate was only 0.12% higher when imputing the lowest SD values instead of imputing the average SD values (as was performed in the original meta-analysis). Similarly, the largest SD sensitivity analysis (**Figure 15**) showed that the effect estimate was 0.30% higher when imputing the highest SD values instead of the average SD values. Importantly, the heterogeneity associated with imputing the lowest SD ( $I^2 = 70\%$ ) was greater than in the original meta-analysis, while it remained the same when imputing the highest SD ( $I^2 = 38\%$ ).

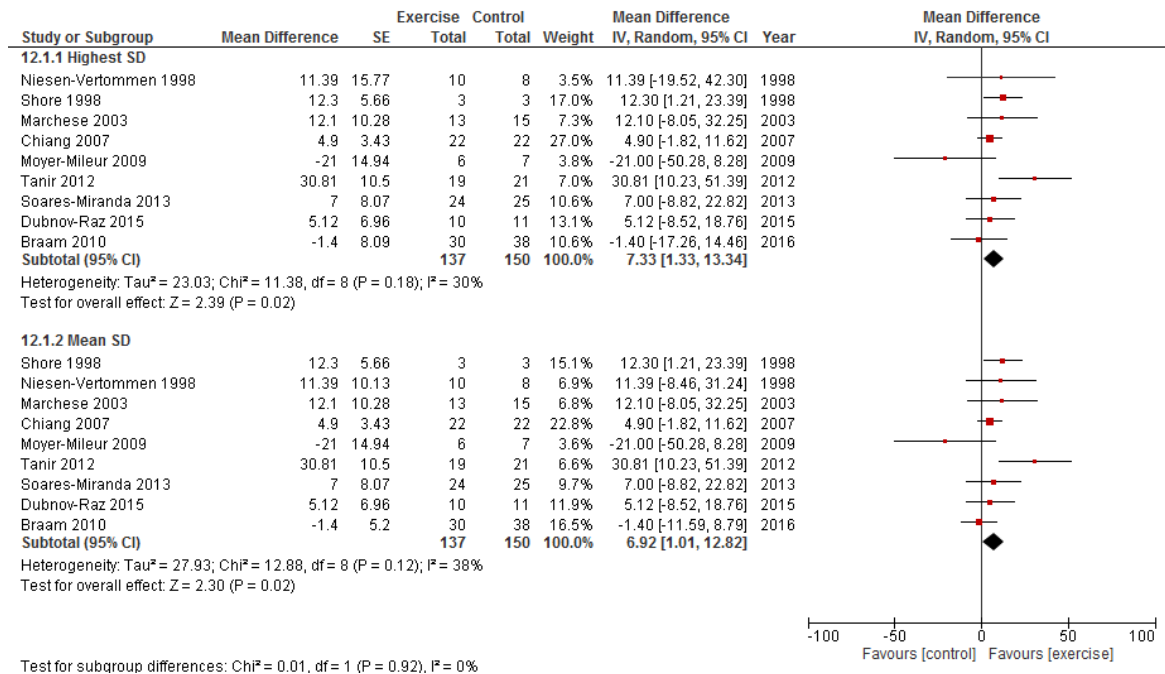
The p-value versus reported SD sensitivity analysis showed that deriving all possible SD values using reported p-values or F-values resulted in a slightly higher pooled effect estimate than using all of the reported SD values (%MD = 7.22 versus %MD = 6.92). Statistical significance was preserved in the former subgroup (p-value = 0.03) and the level of heterogeneity was the same for both subgroups ( $I^2 = 38\%$ ). This comparison is illustrated in **Figure 16**.

Finally, the change score p-value sensitivity analysis showed that only including studies that have either reported or derived SD values associated with change scores

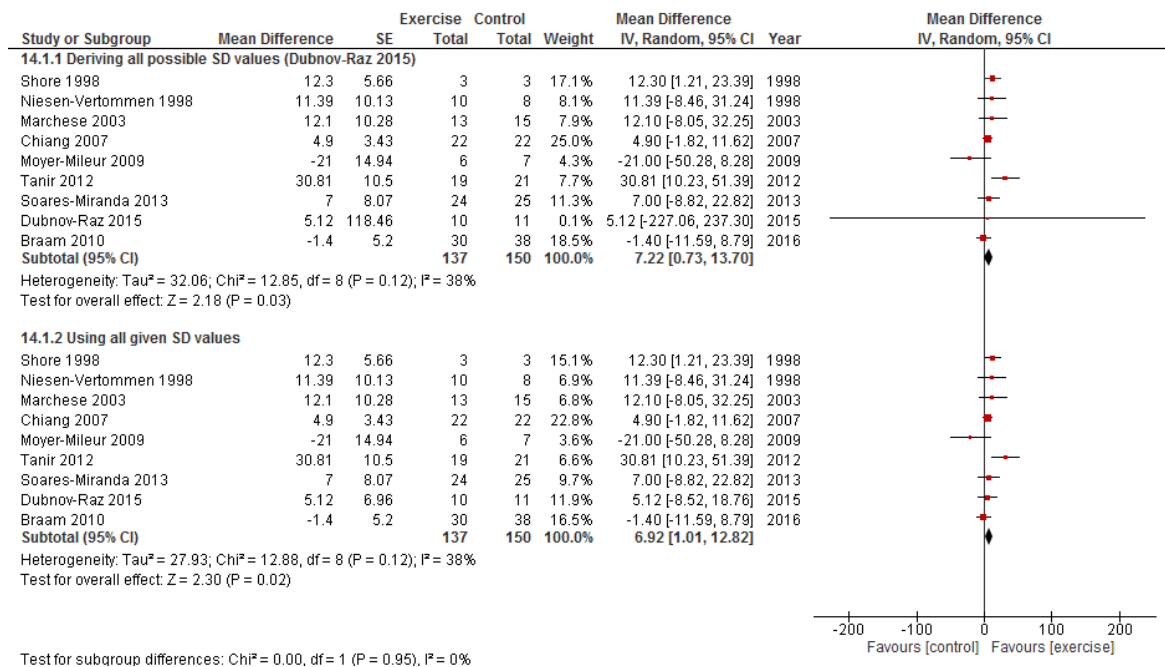
resulted in a slight decrease in the effect estimate (%MD = 6.19, 95% CI -1.12 to 13.50, p-value = 0.10) when compared to the original pooled effect estimate (%MD = 6.92, 95% CI 1.01 to 12.82, p-value = 0.02). This comparison is illustrated in **Figure 17**. The sensitivity analysis also showed that statistical significance for the effect estimate was lost when only including studies for which SD values for change scores were reported or could be derived.



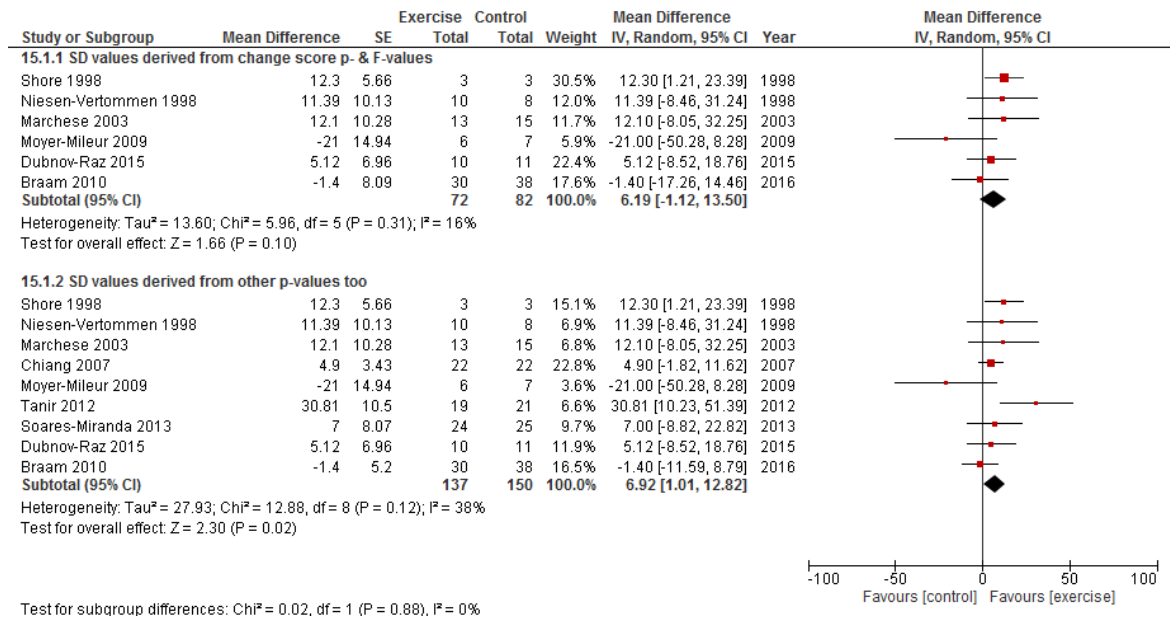
**Figure 14:** Forest plot for sensitivity analysis of imputing lowest SD instead of mean SD



**Figure 15:** Forest plot for sensitivity analysis of imputing highest SD instead of mean SD



**Figure 16:** Forest plot for sensitivity analysis of deriving all possible SD values using reported p-values or F-values versus using the reported SD values



**Figure 17:** Forest plot for sensitivity analysis of only using SD values derived from change score p- & F-values versus using SD values derived from other p-values too

## Chapter 5: Discussion

### I. Summary of Main Results and Comparison to Existing Literature

Since the discovery of cardiac side effects associated with anticancer treatment more than 40 years ago,<sup>94</sup> relatively few clinical studies have directly explored the cardioprotective potential of non-pharmacological therapies.<sup>41,242</sup> In the general population, aerobic exercise is a non-pharmacological preventative and rehabilitative therapy which has been shown to improve various cardiac and CV outcomes, including morbidity and mortality,<sup>57,146</sup> CVD risk factors,<sup>146</sup> and CPF.<sup>155,169</sup> While numerous animal studies have directly examined the cardioprotective benefit of aerobic exercise against cancer treatment (especially AC),<sup>179</sup> clinical studies are mostly limited to offering indirect evidence of cardioprotective benefit, in the form of improved CPF. Furthermore, only a few of these studies have examined the effect of aerobic exercise on CPF in CCS, despite the beneficial effects that have been observed in adult cancer survivors,<sup>77,78</sup> and the growing body of evidence in support of PA as preventative medicine in the general childhood population.<sup>141,243,244</sup> This review provides the first comprehensive collection of the existing studies that used controlled designs to specifically examine the effect of an intervention with an aerobic exercise component on a common cardiac outcome in CCS (i.e., CPF), thus providing possible indirect support for the cardioprotective potential of aerobic exercise.

The main purpose of this systematic review and meta-analysis was to synthesize the existing evidence of the effect of an aerobic exercise intervention on CPF in CCS treated with a known cardiotoxic agent. In brief, the nine included studies and the analyses of their cumulative findings showed a statistically (p-value < 0.05) and a potentially

clinically (MD in relative VO<sub>2</sub> peak >1 ml/kg/min)<sup>1-3</sup> significant effect of an aerobic exercise intervention on CPF, when compared to the change in CPF experienced by a control, standard of care group.

**a. Possible Lower Effect in Childhood Cancer Survivors than in Healthy Children**

Of note, the current review found a pooled increase in CPF of 6.92%, in favour of the exercise group (p-value = 0.02). By comparison, one review of the effect of aerobic exercise in healthy children found that VO<sub>2</sub> peak increased on average 5-6% (or as much as 8-10% in the studies that showed a significant training effect).<sup>238</sup> Another review found that aerobic training in healthy subjects <14 years old increased VO<sub>2</sub> peak values by 7-26% (with the caveat that most studies only showed changes equal to or below 11%).<sup>239</sup>

Another specific finding is that pooling of the individual MD values from the six maximal test studies suggested that an aerobic exercise program may be responsible for a clinically significant change in relative VO<sub>2</sub> peak. The threshold for clinical significance used in this review (i.e., MD in relative VO<sub>2</sub> peak >1 ml/kg/min) is based on the findings of two previous studies in adults that reported the association between incremental changes in CPF and cardiac mortality,<sup>240,241</sup> and one review that summarized the documented association between CPF and the risk of CHD/CVD.<sup>242</sup> Importantly, the two studies found that an increase in VO<sub>2</sub> peak of as little as 1 ml/kg/min corresponded to a decrease in the incidence of cardiac mortality by 9-10% (over a median follow-up of 4.5-7.9 years),<sup>240,241</sup> while the review found that the same increase in relative VO<sub>2</sub> peak was associated with a greater than 5% CVD risk reduction.<sup>242</sup> However, despite this positive

finding, a past meta-analysis of studies in healthy children found that an endurance-type exercise intervention contributed to a larger increase in  $\text{VO}_2$  peak (i.e., approximately 2 ml/kg/min) with the contributing effect sizes not affected by sex, exercise parameters, or test mode.<sup>243</sup> That being said, the cut-off for clinical significance used in this review, while not based on data from studies in children,<sup>1,2</sup> was used since it was a documented relative incremental change in CPF associated with both cardiac morbidity,<sup>1</sup> or mortality.<sup>3,4</sup> By contrast, studies in children that report cardiac outcomes primarily have primarily focussed on setting absolute thresholds of CPF that are associated with lower CVD risk (i.e., 37-40 mL/kg/min for girls, and 40-44 mL/kg/min for boys).<sup>2</sup> Unfortunately, these relative thresholds are not germane to setting a clinical threshold for CCS, since the thresholds were on average much higher than the post-intervention relative  $\text{VO}_2$  peak values attained by participants in all of the included studies in this review.<sup>14</sup>

Together, both findings suggest that aerobic exercise may have a significant effect on CPF in CCS, but that its absolute effect may not be quite as high as in the age-matched healthy population, which is agreeable with some past research.<sup>157</sup> However, given the wide range of aerobic exercise parameters implemented in the included studies (i.e., moderate-high intensity, 6 weeks-12 months in duration, 30-180 minutes/week), it may also be that this pooled estimate is either over- or under-estimated.

There are a few reasons that an aerobic exercise intervention could have been expected to yield a larger absolute increase in relative  $\text{VO}_2$  peak than a similar intervention in healthy samples. The first is that it is well documented that CPF in CCS is on average significantly lower than the age-matched healthy population.<sup>70</sup> The other is



that since the aforementioned reviews of aerobic exercise in the healthy population were completed (the most recent being in 2003),<sup>238</sup> the average baseline CPF among children has declined,<sup>244</sup> which may mean that CCS are likely to have even lower baseline CPF than before. Both of these factors point to an exercise intervention causing a larger increase in CPF in age-matched cancer survivors since it has been previously established that individuals with a lower initial CPF demonstrate a larger increase in CPF following aerobic exercise.<sup>245</sup> However, these reasons to expect a greater increase in CPF among present-day CCS do not preclude the existence of an irreversible effect of cardiotoxic therapy on the heart.<sup>114,246</sup> Thus, in corroboration with past findings,<sup>157</sup> the findings of this review may imply that the impact of the irreversible damage caused by cardiotoxic therapy may be at least partly contributing to the reduced “trainability” of CPF, even in participants with low baseline CPF.

#### **b. Possible Lower Effect in Childhood Cancer Survivors than in Adult Cancer Survivors**

The results of this review also suggest that the effect of aerobic exercise on CPF is lesser among CCS (MD in relative  $\text{VO}_2$  peak = 1.39 ml/kg/min, in current review) than among their adult cancer survivor counterparts (MD in relative  $\text{VO}_2$  peak = 2.90 ml/kg/min and 3.13 ml/kg/min in reviews by Jones et al,<sup>76</sup> and Beaudry et al,<sup>77</sup> respectively). While the aforementioned reasons exist for a lesser observed absolute MD in CPF among CCS than their age-matched healthy counterparts, there are several additional reasons for CCS reporting less CPF benefit from aerobic exercise than adult cancer survivors.<sup>76,77</sup> These reasons may be categorised as one of the following: (1) innate clinical differences between children and adults (i.e., differences in trainability of CPF; and differences in physiological responses to cancer and/or its treatment); and/or (2)

significant differences in some of the characteristics of the interventions used (i.e., aerobic exercise parameters; and combined exercise).

The first possible explanation for the lower pooled point estimate from the CCS studies is that CPF in CCS is not as easily influenced by aerobic exercise as it is in adult cancer survivors (i.e., children with cancer have lower trainability). Not to be confused with the possible explanation for the lower trainability of CCS compared to their age-matched healthy counterparts (i.e., the posited irreversibility of direct cardiac damage), this potential explanation is based on the theory of a maturational threshold in the trainability of CPF (otherwise known as the “Trigger Hypothesis”).<sup>247,248</sup> This theory has been previously supported by the findings of a few studies that have shown minimal or no exercise-induced change in CPF in children from the healthy population.<sup>238,249,250</sup> However, the existence of the maturational threshold posited by the Trigger Hypothesis is still being debated.<sup>251,252</sup> Furthermore, the Trigger Hypothesis has not been examined in any clinical populations to date.

Another possible explanation for the lower improvement in CCS than adult cancer survivors is the moderating effect of body mass on the CPF response to aerobic exercise. This is supported by the finding of a previous systematic review that found adolescent and adult survivors of pediatric ALL are at increased risk of being overweight/obese.<sup>253</sup> If this was the case for the participants in some of the studies included in this review, specifically those that recruited participants following treatment completion, it is possible that a higher body mass would have impeded the capacity for these children to experience exercise-induced improvements in CPF. In support of this, a previous study of adult cancer survivors found that body mass was a significant moderator of the effect of

aerobic exercise on CPF.<sup>254</sup> However, this explanation is challenged by the fact that increased prevalence of overweight/obesity may equally be an issue in some adult cancer survivor populations.<sup>255,256</sup> What is needed to determine whether body mass is a greater threat for impeding the benefit of aerobic exercise in CCS is a comparison of body mass changes over the course of treatment between CCS and adult cancer survivors. This would allow for the exploration of the age-specific impact of body mass changes on exercise-induced changes in CPF.

The relatively lower MD observed in this review when compared to adult cancer survivor reviews may also be attributable to the potential disruption of normal physiological growth and development experienced by CCS, which is not experienced by their adult cancer survivor counterparts. Some examples of potentially inhibited physical maturation due to cancer or anticancer treatment may include a depleted number of cardiac progenitor cells,<sup>257</sup> which are thought to participate in myocardial growth during adolescence;<sup>129,258</sup> the impairment of alveoli maturation;<sup>259</sup> the inhibition of thoracic cage growth;<sup>259</sup> and damage to the developing musculoskeletal system during periods of rapid growth (i.e., less than 6 years of age, or puberty).<sup>260</sup> All of these impairments would at least somewhat limit functioning of one of the systems involved in the oxygen cascade, consequently negatively impacting CPF.<sup>156</sup> Therefore, CCS may not be equipped with fully functioning systems capable of adapting to exercise-induced stress in the same way as adults.

Other than the general possibility that CCS may innately have a lower trainability than adult cancer survivors, it may alternatively be the case that the exercise protocols in the included studies were too strenuous, especially for this age population, and therefore

resulted in low adherence. In order to explore this theory, the overall volume of exercise was calculated for all studies that provided sufficient information to do so (n=8).<sup>192,193,195–199,218</sup> The calculation used to do so was: exercise volume = session duration (minutes/session) × frequency of intervention (sessions/week) × intervention length (weeks/intervention). When compared to the adult cancer survivor study with the highest volume of aerobic exercise (i.e., 1272 minutes),<sup>261</sup> as many as six of the included studies in this review prescribed higher volumes of exercise, at comparable intensities, to some or all of its participants (**Chapter 4, Table 2**).<sup>192,193,195,197–199</sup> Interestingly, the doses of aerobic exercise used in the included studies were either within or below the range of doses recommended by POEM.<sup>69</sup>

In considering the possibility of volume affecting adherence, it is also important to note that the use of moderate-intensity exercise in the CCS studies may have resulted in a degree of non-adherence. It has been stated previously, that in addition to not being as threatening or fatiguing as moderate-intensity regimens, lower intensities (i.e., as low as 20% of HR<sub>max</sub>) may also be beneficial in CCS.<sup>262</sup> In support of administering lower intensity exercise to improve CPF, Swain and Franklin<sup>245</sup> reported that for subjects with a low baseline fitness level, an intervention with an intensity of 40% of the VO<sub>2</sub> max (i.e., approximately 55% of HR<sub>max</sub>) is still capable of increasing CPF.<sup>245</sup> Unfortunately, since adherence was not reported consistently across any of the included studies, it is not possible to conclude whether or not there is an indirect correlation between any intervention parameter and the lower pooled effect estimate reported for the CCS studies.

Nonetheless, it may be hypothesized that aerobic exercise programs with lower intensity and higher weekly and overall volume would be effective at improving CPF

among CCS. Unfortunately, this hypothesis has received little attention in cancer survivors, let alone CCS. In fact, the overview by Buffart et al,<sup>172</sup> which described all studies that directly compared different exercise parameters (not including time per session) in cancer survivors, only indicated one study that was relevant to determining optimal intensity for improving CPF (with non-significant findings)<sup>263</sup> and none that were relevant to determining optimal weekly volume. Furthermore, the combination of a relatively low weekly volume of exercise, and either an equal or relatively high intensity in more than half of the included studies,<sup>177,193,195-197</sup> does not seem to be explicitly rationalized by either POEM recommendations, nor by any of the included studies. It should be noted that a recent study in adult cancer survivors may contest the effectiveness of lower intensity aerobic exercise for producing a sustained cardiopulmonary benefit.<sup>264</sup> However, this study did not examine the moderating effect of concurrently increasing volume. This is something that should be explored directly in future controlled studies on the effect of aerobic exercise on CPF in CCS.

It is also possible that the relatively higher proportion of studies that used combined interventions (i.e., aerobic and strength training) in this review is responsible for the lower improvement in CPF. Specifically, seven out of nine included studies in the current review used combined interventions, whereas only one out of six studies in the review by Jones et al,<sup>76</sup> and only six out of the 18 studies/comparisons in the review by Beaudry et al<sup>77</sup> included a combined intervention group. This possibility is supported by the review of Saavedra et al,<sup>265</sup> which found that overall, combined programs actually failed to achieve improvements in aerobic fitness in obese children. By contrast, this theory is challenged by Courneya et al,<sup>266</sup> who found that there was no significant difference

between an aerobic exercise intervention and a combined intervention in the effect on CPF, in a group of breast cancer survivors. A few other studies have also reported larger improvements in functional fitness for a combined intervention than an aerobic intervention among healthy older adults,<sup>267</sup> which may translate to a larger effect of combined treatment on CPF, rather than what is suggested by the current review. That being said, adherence has previously been shown to be lower for combined interventions than solely aerobic exercise interventions, in adult cancer survivors.<sup>254,266</sup> Therefore, it is possible that low adherence, mediated by a combined intervention, is the underlying reason for the lower effect estimate in the current review.

### **c. Final CPF in Cancer Survivors Remains Below CPF in Healthy Children**

When compared to the 50<sup>th</sup> percentiles for a healthy age- and sex-matched Canadian,<sup>268</sup> American,<sup>269</sup> or European child,<sup>270</sup> as well as the reference values from Bar-Or and Rowland,<sup>271</sup> the post-intervention VO<sub>2</sub> peak values obtained by the exercise groups in the included maximal test studies were consistently lower (range: 25.2-37 ml/kg/min).<sup>192,193,197-199,218</sup> In one of the included studies (**study 3**)<sup>198</sup>, it was even found that out of 24 participants in the exercise group, more than half had a post-intervention VO<sub>2</sub> peak of  $\leq 2$  SDs below the pediatric normative values for that country. This failure to meet normative values, even after an exercise intervention, is in agreement with the deficit in VO<sub>2</sub> peak observed in long-term CCS. For example, the review by van Brussel et al<sup>70</sup> found the deficit in relative VO<sub>2</sub> peak was 6 ml/kg/min among long-term survivors of childhood ALL. A similar deficit has also been reported for long-term female survivors of other types of childhood cancer (e.g., acute non-lymphoblastic leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and Wilms' tumour).<sup>71</sup>

It should also be noted that the observation of a deficit in CPF among CCS may not be limited to studies of long-term CCS, as related studies with adult cancer survivors have also shown an acute deficit in CPF during treatment, or shortly after treatment cessation. One example is the study by Dolan et al,<sup>72</sup> which measured VO<sub>2</sub> peak both at baseline (prior to treatment initiation) and at the end of chemotherapy, and showed that it decreased even over the course of chemotherapy.<sup>72</sup> Another example is a study by Jones et al,<sup>272</sup> which examined breast cancer patients during and after adjuvant therapy, and found that post-treatment they had the predicted VO<sub>2</sub> peak of healthy women (i.e., without a history of breast cancer) 20-30 years older than them. This finding was supported by a subsequent review.<sup>273</sup> Similarly, the acute effect of cancer treatment on CPF was reported in the control group of one of the included studies in this review.<sup>199</sup> These findings collectively suggest the following: (1) there is a significant difference in CPF between children who have received treatment for cancer and their healthy controls; (2) that this difference may become apparent shortly after treatment begins (i.e., acutely); (3) the difference may be sustained over time (i.e., long-term); and (4) the exercise interventions studied to date have been incapable of fully “restoring” CPF among CCS to the level of the healthy age-matched population.

There are several possible reasons that aerobic exercise has been unsuccessful at completely reversing the deficit in CPF in CCS. One possible reason stems from the previously mentioned theory that the exercise interventions being used in these studies are resulting in substantial levels of non-adherence. This precludes the exercise interventions from being able to effectively restore the VO<sub>2</sub> peak values of the participants. Another possible explanation is that the improvements from baseline to final

values (i.e., the change scores) observed for the exercise groups in the included studies represents the extent to which exercise is capable of reversing the deficit in CPF caused by deconditioning.<sup>158,274</sup> The remaining discrepancy may be due to the existence of irreversible cardiac damage that has been caused by treatment-related CT prior to exercise initiation,<sup>114,246</sup> which as previously mentioned may be partly contributing to the reduced “trainability” of CPF among CCS. This possibility was first suggested in the seminal study by Sharkey et al,<sup>157</sup> which showed that although an aerobic exercise intervention was capable of increasing CPF in CCS, it was not able to return cardiac output to a normal level for an age-matched healthy subject. Therefore, it is possible that this damage could have only been avoided had the exercise intervention been implemented earlier. In support of this, there are a few studies in the adult cancer survivor population that have shown that an aerobic exercise intervention administered during cancer therapy is able to prevent both the occurrence of pathological ECG findings,<sup>275</sup> and blunt the decline in VO<sub>2</sub> peak,<sup>276</sup> as compared to a matched control group of during-treatment cancer survivors.

The results of this review may in fact support the latter hypothesis, considering that the change score of the control group for the only included study that recruited and enlisted participants pre-treatment (**study 4**),<sup>199</sup> is the largest negative change out of all the studies, and the change scores for the control groups in all included studies that implemented aerobic exercise post-treatment are positive.<sup>192,196–198</sup> Furthermore, the exercise group in the former study demonstrated a 0 ml/kg/min change score, which may be interpreted as blunting the decline in CPF (i.e., the decline is prevented altogether). However, since the participants in **study 4** began the exercise intervention at the



beginning of their cancer treatment regimen (before cancer treatment could affect CPF), but still had below-average baseline CPF (25.2 mL/kg/min; 50<sup>th</sup> Percentile for European children approximately the same age = 45.4 mL/kg/min for girls and 46.7 mL/kg/min for boys),<sup>199,270</sup> their full discrepancy with age-matched reference values cannot be attributed to either direct or indirect effects of cancer treatment. Therefore, the control group in this study may not offer an accurate model of the independent effect of cancer treatment on CPF.

#### **d. Subgroup Analyses**

##### **i. Treatment Status**

In contrast to the finding of significantly greater benefit of post-treatment aerobic exercise on CPF (p-value < 0.00001), by Jones et al,<sup>76</sup> and in agreement with the insignificant findings of the more recent review by Beaudry et al,<sup>77</sup> the treatment status subgroup analysis conducted in this review did not show a significant difference between subgroups (p-value = 0.70). It can be hypothesized that the lack of significance found by this subgroup analysis may be at least partially related to the lower amount of overall heterogeneity detected between the effect estimates of the included studies in this review (i.e.,  $I^2=38\%$  in this review versus  $I^2=87\%$  in the review by Jones et al.,<sup>76</sup> and  $I^2=63\%$  in the review by Beaudry et al<sup>77</sup>). The lack of significant difference may also be partially due to the high amount of heterogeneity detected in the effect estimates of the studies in the post-treatment group ( $I^2=62\%$ ), and the inclusion of a heavily-weighted study in this subgroup, that reported an MD in favour of the control group.<sup>198</sup> Although one of the studies in the “during treatment” subgroup also included some participants that had already completed cancer treatment,<sup>193</sup> this subgroup registered a far lower amount of

heterogeneity ( $I^2=19\%$ ). Therefore, the effect estimate of this one included study was not perceived as substantially heterogeneous compared to the effect estimates of the other included studies in this subgroup.<sup>194,195,199,218</sup>

Despite the fact that the subgroups in this analysis were not significantly different from one another, it should be noted that the p-value for the %MD of the during treatment subgroup approached significance (%MD: 6.52, p-value = 0.05), and was only slightly lower than the effect estimate from all included studies (%MD: 6.92, p-value = 0.02). This finding suggests that it is possible that the combination of studies within this subgroup provides a more reliable pooled estimate of the effect of exercise on CPF for this specific treatment status than the overall effect estimate for all included studies. It also suggests that aerobic exercise applied during treatment is an effective strategy to mitigate a decline in CPF in CCS. Furthermore, the decrease in the pooled effect estimate for this subgroup relative to the overall effect estimate was not surprising given that smaller improvements in  $VO_2$  peak are expected during treatment.<sup>277</sup>

That being said, it should be noted that in some of the included during treatment studies, the expected decrease in CPF was not observed in the control group.<sup>195,218</sup> It is likely that the control groups in these studies had already experienced an acute decline in CPF following cancer treatment initiation and were possibly experiencing an increase in CPF due to their involvement in the study (i.e., some contamination due to changes in PA behaviours attributable to the 'Hawthorne effect'). Therefore, it will be necessary for future studies in CCS to start the measurement of CPF prior to beginning cancer treatment, in order to determine a more precise estimate of the complete mitigating effect

of an exercise intervention on CPF during treatment, relative to the established negative CPF outcomes in CCS who do not receive any intervention.<sup>70</sup>

#### ii. Intervention Length

As for the intervention length subgroup analysis conducted in the current review, while not statistically significant, the result was that shorter intervention lengths had a greater effect on CPF than longer interventions (p-value = 0.51). A similar subgroup analysis performed by Jones et al,<sup>76</sup> (i.e., intervention length <4 months versus intervention length  $\geq$ 4 months), reported a significant difference between subgroups (p-value < 0.001), with shorter interventions also being associated with a greater improvement in CPF. The reason for the shorter interventions having a greater effect in the current review may be the same as that for the subgroup analysis performed by Jones et al,<sup>76</sup> namely, that the majority of the studies with longer interventions were also performed during treatment. It is important to note that in this review, while the shorter intervention subgroup produced a significant p-value for the effect estimate (p-value = 0.04), this subgroup effect estimate should not necessarily be interpreted as a closer approximation of the true effect for interventions  $\leq$ 3 months in length, since heterogeneity within this group is higher than the heterogeneity detected for the overall effect estimate (i.e.,  $I^2=56\%$  vs.  $I^2=38\%$ , respectively).

#### iii. Maximal versus Submaximal Exercise test

One interesting finding from the *post-hoc* exercise test subgroup analysis was that the submaximal test subgroup showed a much higher (albeit not statistically different) pooled %MD than the maximal test subgroup (p-value = 0.79). It is possible that this is a result of submaximal tests being less accurate or reliable in measuring CPF, and being less able

to accurately detect smaller changes in CPF following an aerobic exercise intervention.<sup>278,279</sup> This hypothesis is supported by the high amount of heterogeneity detected in this subgroup ( $I^2=75\%$ ). However, if it can be assumed that the accuracy or reliability of submaximal tests is not an issue (i.e., the reported correlation coefficients from the age-matched validation studies were sufficiently high), than this finding may alternatively be indicative of maximal tests underestimating the true effect of an aerobic exercise intervention on CPF in CCS. Maximal tests may underestimate the effect because of either limitations in one or more of the other systems that contribute to performance of this type of exercise test (e.g., respiratory system,<sup>280</sup> neuromuscular system<sup>281</sup>), or because of varying effort levels at different measurement points (i.e., higher effort at baseline than post-intervention CPF measurement), which is ultimately an issue with administration of the procedure.

There are also confounding differences that exist between these subgroups, which may have contributed to the result of this subgroup analysis. One of these differences is that four of the six maximal test studies used a supervised intervention, while all three submaximal test studies used a home-based, un-supervised intervention. Given this difference, the finding of this subgroup analysis is in disagreement with the findings of previous studies in both the age-matched non-cancer population,<sup>282</sup> and the cancer survivor population (adults<sup>283</sup> and children<sup>284</sup>), that suggest supervised exercise is more effective when compared to non-supervised exercise. In fact, the authors of one of the included studies previously found that using a maximal test to directly measure  $VO_2$  peak, in addition to using a supervised exercise intervention, showed a significant

improvement in VO<sub>2</sub> peak,<sup>284</sup> in comparison to using a submaximal test (9-MRW test) with a home-based exercise intervention.<sup>194</sup>

On the other hand, this finding is in line with the results of one of the subgroup analyses completed in the review by Beaudry et al,<sup>77</sup> which found that adult cancer survivors experienced superior improvements in CPF when individualized exercise programs were used, as opposed to group/class-led exercise interventions (p-value = 0.003). A possible explanation for this subgroup analysis result are the negative associations children have with receiving therapy related to their cancer (even if it is not directly related to treating the malignancy), associations they may make more strongly with a supervised, class-led intervention than an un-supervised, home-based intervention. Thus, it is possible that a home-based, individualized intervention would be more effective for this population in some instances, despite the lack of supervision, particularly if adherence was an issue for the supervised exercise interventions.<sup>77</sup>

It should also be considered that perhaps the six studies that used maximal tests may not be based on a cumulative sample that is truly representative of the CCS population. Given some of the exclusion criteria for the included maximal test studies (e.g., the presence of any chronic disease;<sup>192</sup> known cardiac dysfunction;<sup>192,196</sup> and receiving bone marrow transplantation and/or growth hormone<sup>198</sup>) this is a reasonable suspicion. It should also be noted that the submaximal tests that were used in the included studies have both been validated in an age-matched population. Therefore, although maximal tests may be superior in some cases (i.e., where CCS do not have known symptomatic heart conditions),<sup>280</sup> submaximal tests may still have their place for CCS that do not meet these criteria, as long as they can be shown to be sufficiently precise and reliable.

## II. Quality of the Evidence

### a. GRADE Scoring

As already stated, the quality of evidence on the effect of aerobic exercise on CPF in the included studies was graded according to the GRADE approach.<sup>191</sup> There are a number of advantages to using this approach compared to other approaches for grading evidence quality.<sup>285</sup> Specifically, the GRADE approach uses explicit definitions of overall quality of evidence, and the judgements in GRADE are based on more than study design. A more complete list of advantages are outlined in the commentary by Oxman.<sup>285</sup> Based on the GRADE approach, the overall quality of the evidence provided by the studies included in this review (both for all nine studies combined, and for the six studies that reported CPF in terms of VO<sub>2</sub> peak) was low.

Since five out of the nine included studies were RCTs, and the other four were CCTs, the initial scoring of the evidence (based on the ‘study design’ factor) was high. Although it has previously been suggested that including CCTs increases the risk of exaggerating the true effect of an intervention, due to the possibility of unaccounted-for and un-randomized confounders introducing selection bias,<sup>286</sup> a past review found that the incidence of selection bias in reviews that included CCTs is inconsistent at best.<sup>287</sup> Furthermore, since three of the four CCTs used matching of groups in order to control for certain baseline demographic characteristics (**studies 1, 8 and 9**),<sup>192,218,197</sup> which RCTs similarly did via stratification, the risk of selection bias is relatively low for the former studies. Consequently, the GRADE approach specifically details that these “quasi-RCTs” may be judged as providing high quality evidence, in the absence of important limitations.<sup>191</sup> That being said, it should still be considered that all studies included in this

review (CCTs and RCTs) may still be at risk for at least partial selection bias, as even in those studies that matched/stratified groups for some baseline characteristics, there is the risk that they differed on other important characteristics at baseline.

Upon review of the quality factors that could have decreased the quality of evidence,<sup>285</sup> the quality of evidence was downgraded by two levels. Specifically, the quality of evidence was downgraded by one level on the basis of study limitations (aka risk of bias) and by another level based on imprecision. The risk of bias downgrading was based on two main sources of concern: (1) the potential for baseline imbalance between the control and exercise groups; and (2) the unaccounted-for attrition rates. Meanwhile, the imprecision downgrading was based on the fact that neither of the criteria for precision outlined in the GRADE handbook were met by the included studies.<sup>191</sup> These criteria not being met can be attributed to both how few studies were included in the review, and the small numbers of participants included in most of these trials. The latter is common in the paediatric population, and for newly introduced interventions.

The quality of the evidence was not downgraded by any more levels for inconsistency; indirectness; or publication bias (since the funnel plots and the linear regression analyses both indicated no publication bias), nor was it upgraded on any of the factors that could have increased the quality of evidence.<sup>191</sup> While one may think that downgrading by at least one level for indirectness would be warranted since the outcomes of CPF and relative VO<sub>2</sub> peak are both still indirect measures of cardiac damage and/or cardioprotection, this was not the case, as it was pre-specified that CPF was the outcome of interest. Therefore, CPF was a direct outcome for this specific review.

Lastly, it is important to remember that while the discrete judgements for each factor do contribute to the overall quality of evidence for a specific outcome in an additive way, grading quality of evidence according to the GRADE approach involves judgements that are not mutually exclusive. Therefore, in this sense, GRADE is not a quantitative approach to assessing the quality of evidence.<sup>191</sup>

### **b. Clinical Heterogeneity**

Although the measurement of clinical heterogeneity between the effect estimates of the included studies ( $I^2 = 38\%$ ) is at most moderate based on the cut-offs included in the Cochrane Handbook (0-40% = not important; 30-60% = moderate; 50-90% = substantial; 75-100% considerable),<sup>288</sup> the heterogeneity in this effect estimate is still a cause for concern, given that the upper limit of the CI of the  $I^2$  (0%, 86%) surpasses the cut-off for considerable heterogeneity. Therefore, further investigation of the potential sources of heterogeneity between studies is justified for this reason. Unfortunately, a few difficulties with conducting participant-specific subgroup analyses arose due to the results of the systematic review. Firstly, unlike other subgroup analysis factors that were relatively homogeneous within individual studies, and heterogeneous across studies, other participant-specific characteristics had significant levels of variability within individual studies in this review. Specifically, some studies contained participants with a variety of different primary cancer diagnoses, and primary cancer treatments. Furthermore, for some participant-specific (e.g., baseline exercise levels), intervention-specific (e.g., adherence levels), and study design-specific subgroup analysis factors (e.g., amount of follow-up), there was insufficient data to place all studies in a specific subgroup.



Of the original *a priori* subgroup analyses, plus two *post hoc* subgroup analyses, two subgroups showed an effect estimate that was trending towards significance: the  $\leq 3$  months subgroup ( $P=0.07$ ;  $I^2 = 66\%$ ); and the during treatment subgroup ( $P=0.05$ ;  $I^2 = 19\%$ ). Two others displayed a significant effect estimate: the non-validation subgroup ( $P=0.03$ ;  $I^2 = 0\%$ ); and the maximal test subgroup ( $p=0.03$ ;  $I^2 = 0\%$ ). Unfortunately, both subgroups that showed marginal significance, also had measurable clinical heterogeneity in their effect estimates (one study had substantial heterogeneity), and all four subgroups were not statistically different from the other subgroup included in their respective subgroup analyses.

There are also other factors that may have indirectly contributed to some heterogeneity in the pooled effect estimate, but that were not investigated using subgroup analyses because of their speculative nature. An example is the difference in length of the studies. The variation in length of study could conceivably have been a source of heterogeneity if it led to some of the studies being more affected by seasonal variation in PA behaviours than others. Specifically, those studies that lasted a shorter period of time, and did not examine patients equally over all 4 seasons, such as **study 2**<sup>193</sup> which examined participants primarily in the summer months, may have had participants that were more affected by seasonal variation, leading to either an over- or underestimation of the effect of the exercise intervention on CPF.<sup>193,196,218</sup>

### **c. Appropriateness of CPF**

Another important consideration when determining the quality of the evidence provided in the review is whether or not the chosen outcomes and the data available for these outcomes, are appropriate for addressing the aim of the review. Firstly, the

appropriateness of CPF as the primary outcome for this review (i.e., a potential surrogate outcome for cardiac function) is directly supported by the instructions in the GRADE Handbook, which state that use of a surrogate outcome should be reserved for reviews where evidence on the population-important outcome (in this case, cardiac structure and function) is lacking, which it happens to be presently.<sup>191</sup> CPF is an ideal choice in the absence of sufficient data on a more direct measure of cardiac function, since CPF has been correlated with direct outcomes of cardiac structure and function in the general population (i.e., those with normal LVEF),<sup>289,290</sup> as well as the cancer survivor population,<sup>159,163</sup> including one study that was included in this review.<sup>197</sup>

Furthermore, CPF is also a population-important outcome in its own right. It has previously been labelled as an important independent marker of both functional ability and CV health.<sup>291–293</sup> The importance of exercise testing and the determination of VO<sub>2</sub> peak increased when it became apparent that resting cardiac function measures cannot reliably predict exercise performance and functional capacity, and that exercise tolerance is a more predictive, and holistic metric of health in cardiac patients.<sup>294,295</sup> In fact, CPF is recognized as a stronger predictor of mortality than established risk factors, in both the general population, and the cardiac clinical population.<sup>75</sup>

Lastly, the importance of CPF as an outcome of interest in CCS is supported by the attitudes of cancer patients towards their physical needs following cancer diagnosis and treatment. Patient values are one of three main factors that should be considered when determining the effectiveness of an intervention, the other two being clinical expertise and evidence. Therefore, taking the values of CCS regarding CPF into consideration is key both in the context of this review, as well as in the future determination of the

appropriateness and effectiveness of an aerobic exercise intervention compared to other interventions.<sup>191</sup> In one study, it was found that having physical needs met was among the highest priorities for most young cancer survivors (or their guardians, in the case where the survivors were deemed too young to rank their own priorities).<sup>296</sup> Additionally, increasing CPF is associated with positive effects on psychosocial factors, which coincidentally, have been shown to be a main determinant of a child's ability to participate in recreational, leisure, or school exercise programs.<sup>297</sup>

### III. Strengths and Limitations

#### a. Strengths of Review

The methodological strength of this review is that it was able to draw upon the best available evidence from almost all of the relevant studies that have been conducted across the globe. Specifically, certain review methods (e.g., contacting authors) allowed for additional unpublished information and data to be included in the review, as well as for clarification on certain criteria not included in the published and/or grey literature. Therefore, the results of this review provide a more complete set of the existing data on the effect of an aerobic exercise intervention on CPF in CCS than what is currently available from the combination of electronic databases, relevant conference abstracts/proceedings, and/or other grey literature sources. In fact, upon screening of a Cochrane review update by Braam et al that had been published since the completion of the search methods for the current review, and the aim of which was broader than my review,<sup>80</sup> it was found that five of the included studies in this review were missing from the former.<sup>1-5</sup> There are three main possible reasons the current review included more studies than the review by Braam et al: (1) some of the 'outcome' search terms used in

this review were much more specific to CPF; (2) the list of ‘intervention’ search terms used in this review was much more specific to aerobic exercise; and (3) this review also searched some databases not searched by Braam et al (e.g., ProQuest, SPORTDiscus, and Web of Science).

Another strength of this review is that it adds power to the content of the existing literature in CCS. Specifically, the pooled effect estimates from this review have more power than the estimates from the included individual studies, and is also more powerful than the pooled effect estimates from the most recent past reviews. To recap, there are three past reviews that have been conducted on studies in CCS, and that are relevant to the focus of the current review, but not as specific.<sup>78-80</sup> The aim of the most recent review (Braam et al<sup>80</sup>) was to review studies that evaluated the effect of a physical exercise training program (not necessarily aerobic) on various outcomes of physical fitness in children within their first five years of cancer diagnosis. Meanwhile, the aims of the other related reviews were to: (1) review the studies that examined any effect of an exercise intervention in CCS (Baumann et al<sup>64</sup>), and (2) review exercise intervention studies aimed at improving physical function or psychological well-being in patients treated for hematological cancer (Liu et al<sup>298</sup>). The current review addressed limitations associated with these previous reviews in that it only included studies with an aerobic exercise component; it used an explicit definition of CPF; it focussed on controlled studies only; it contained studies that enrolled exclusively childhood participants; it included more studies that used a maximal test to measure CPF; and it included five studies that have not been included in any past review (**studies 1, 2, 4, 8, and 9**).<sup>1-5</sup>

A specific strength of some of the studies included in this review is that they potentially suggest the feasibility of maximal testing in CCS. Based on the reporting of adherence in terms of attendance by three of the maximal test studies,<sup>197-199</sup> the employment of maximal testing does not necessarily seem to be associated with low adherence and/or compliance. Specifically, **studies 3, 4, and 9** reported average adherence rates of 92%,<sup>198</sup> 68%,<sup>199</sup> and 78%<sup>197</sup> for its EX participants, respectively. To put this in perspective, previous results in the literature have stated 80-85% is the maximum adherence rate to be expected for exercise programs, even when facilities and attitudes towards exercise are optimal.<sup>168</sup> These adherence levels are also within the range of adherence levels reported by a past review of exercise intervention studies in CCS (67% - 98%).<sup>64</sup>

Lastly, this review is significant in that it contributes to one of the many remaining unanswered questions about exercise as a cardioprotective strategy in cancer survivors: “how effective is aerobic exercise at protecting the heart, based on a common cardiac outcome (i.e., CPF), in CCS treated with a known cardiotoxic agent?” Treatment-induced CT in CCS is a serious and widespread issue in Canada, given the high survival rate among children diagnosed with cancer (83-85% in children diagnosed from ages 0-19 years),<sup>1,25</sup> and the fact that an average of approximately 1300 new childhood cases are diagnosed every year.<sup>3</sup> Moreover, since the most cardiotoxic treatments are mainstays for treating certain childhood cancers,<sup>229</sup> an effective cardioprotective strategy, including one or more cardioprotective therapies, is critical for this population. This is the first systematic review and meta-analysis of the effect of aerobic exercise on CPF that is specific to the CCS population, to the author’s knowledge. Current research on aerobic

exercise as cardioprotection against CT has focussed primarily on adult cancer survivors, specifically breast cancer survivors. In summary, this review informs the existing exercise recommendations for CCS, and may eventually inform future standard of care.

#### **b. Limitations of Review**

There are a number of limitations that are directly related to the review process. One of these is the fact that studies that were written in languages other than English could not be included, due to limited resources, including in one case where the information available in the limited English record (e.g., conference proceeding) strongly suggested eligibility.<sup>303</sup> Similarly, results (final or preliminary) of several studies that were either ongoing or awaiting publication were also not included in the review, due to authors not being willing to share the collected data from these studies.<sup>304-306</sup>

Another limitation is that certain steps in the methods were only completed by one author, due to limited time and personnel (i.e., data extraction and management, assessment of risk of bias, and GRADE scoring). It is possible that using more than one author in these steps would have resulted in different data and information extracted, risk of bias judgements, or GRADE score. Also, time constraints placed on some of the secondary search strategies (i.e., the grey literature search) may have resulted in missing some PE records, as was already mentioned in the results chapter.

Another limitation is related to the decision to base the threshold for clinical relevance on the findings of a few adult cancer survivor studies.<sup>240-242</sup> Although this was not ideal, since these studies are not directly representative of CCS, it was done because the findings of these studies are more relevant than the findings of comparable childhood

studies. Specifically, childhood studies primarily focussed on the absolute cut-offs for CPF that are associated with lower CVD risk, and these cut-offs (i.e., 37-40 mL/kg/min for girls, and 40-44 mL/kg/min for boys) are on average much higher than the post-intervention relative VO<sub>2</sub> peak values attained by participants in all of the included studies in this review, rendering them unsuitable within the context of CPF for CCS.<sup>307</sup>

A final limitation of the review is that many of the subgroup analyses could not be performed due to uneven distribution of the clinical characteristics and intervention parameters across the studies. Therefore, many of the secondary objectives could not be addressed. However, the two other possible subgroup analyses that were determined *post hoc* (i.e., following the search for studies, and the extraction of data) should be considered in future similar reviews in this area. Similarly, it is possible that other sensitivity analyses would have revealed a significant difference in the effect estimate due to potentially arbitrary decisions or cut-offs. That being said, in this review, as in all reviews, the results of the subgroup analyses and sensitivity analyses need to be considered with caution, as it is always possible for the results of these to inform misleading recommendations, no matter how many studies are included in the review and meta-analyses.<sup>288</sup>

#### IV. Implications of Review Findings

The significant positive effect estimate in favour of aerobic exercise, both in terms of %MD (6.92 %) and relative VO<sub>2</sub> peak (1.39 ml/kg/min) is an important step towards the standardization of aerobic exercise prescription in CCS. The implication of this effect estimate is made even more impactful by the fact that previous studies have correlated a similar change in relative VO<sub>2</sub>peak (1 ml/kg/min) with a decrease in CV mortality rate

(9-10% decrease)<sup>240,241</sup> that is comparable to (or greater than) the decrease caused by other cardioprotective strategies (i.e., pharmacological therapies).<sup>41</sup> Specifically, ACE inhibitors, which have been previously studied for their cardioprotective potential in CCS, have been shown to decrease the incidence of CV mortality by as much as 12% in adult patients with hypertension.<sup>308</sup> Beta-blockers, another proposed pharmacological option against CT, have less of a proven effect on CV mortality and in some cases have been shown to result in higher rates of serious adverse events in children with HF.<sup>309</sup> Furthermore, it has been previously reported that beta-blockers have very low compliance rates in adults when compared to other anti-hypertensive therapies due to the adverse events they cause, such as Raynaud's phenomenon, and low pulse rate.<sup>310</sup> Therefore, beta-blockers may not be as effective at preventing CV outcomes as aerobic exercise for this reason as well.<sup>311</sup>

Furthermore, the findings from this review, although not directly demonstrating a cardioprotective effect, are a preliminary step towards establishing the putative cardioprotective effect of aerobic exercise against the direct cardiotoxic impact of cancer treatments. It should be noted that the factors limiting oxygen transport during maximal exercise are: (1) maximal cardiac output; (2) pulmonary diffusion; (3) blood volume and flow; and (4) peripheral factors (i.e., muscle diffusion capacity, mitochondrial enzyme levels, and capillary density).<sup>312</sup> As it has been reported that as much as 70-85% of a decrease in CPF can be attributed to reduced cardiac output,<sup>313</sup> it is highly possible that a positive change in CPF (such as that observed in the included studies) is at least somewhat attributable to a change in cardiac function, as well as an improvement in the function of the lungs, the circulatory system, and/or the muscle tissue.



This review has also highlighted a few ways in which the research in this area is lacking, which has implications for how it can be improved. The main limitation is that the literature consists predominantly of studies with small, and consequently under-powered sample sizes (with the exception of one study).<sup>198</sup> By comparison, the sample sizes in almost a third (n=5) of the adult cancer survivor studies included in the most recent systematic review,<sup>77</sup> are larger than, or equal to the largest sample size among the included CCS studies. This limitation is most likely related to the challenge of upscaling interventional research efforts in CCS. Although challenging, future trials should strive for larger sample sizes in order to minimize the risk of either under- or overestimating the true effect size.

Another limitation of the literature that was identified by this review, is that the results of exercise testing protocols used in some or all of the included studies may not have been representative of the true change in CPF. Specifically, since all of the CPF values reported by the included studies were either based on the results of a maximal test (that was limited by volitional exhaustion), or a predictive submaximal test (which may have equally been compromised by motivation), a difference in the effort level between baseline and post-intervention measurements may have resulted in an inaccurate representation of true change in CPF. One way to control for this possible problem would be to measure effort, and determine whether or not there was a significant difference between baseline and post-intervention effort levels. Unfortunately, none of the included studies reported assessing some measure that is related to peak exertion, and independent of changes in CPF (e.g.,  $HR_{max}$ <sup>247</sup> or RPE<sup>299</sup>) during exercise tests. In addition, the results of the submaximal exercise tests specifically may not be an accurate estimate of the true

change in CPF because they use a different scale of CPF. For instance, one possible reason **study 6** reported such a large effect in favour of the control group (in addition to the possibilities of contamination in the control group, and/or low adherence/high attrition in the exercise group) is that the scale of the submaximal exercise test (PACER) resulted in baseline measurements that were much closer to 0, and subsequently led to disproportionately larger % change scores.<sup>1</sup> Thus, future studies should use one of the aforementioned measures of effort to ensure consistency across CPF measurements before and after an intervention, and use exercise tests with comparable scales.

Related to missing information, the included studies also did not consistently report on all potential modifiers of the effect of aerobic exercise on CPF. For example, it would have been helpful to consider the cardiotoxic risk factors when interpreting the effectiveness of an aerobic exercise intervention on CPF in CCS. Unfortunately, the studies included in this review rarely reported on some of the most important cardiotoxic risk factors for CCS, such as total cumulative dose of cardiotoxic therapy and duration since initiation of treatment.<sup>159</sup> In fact, total cumulative dose of AC was clearly reported by only two of the nine included studies in this review.<sup>193,197</sup> Information related to duration since initiation of treatment was more commonly reported among the included studies, but was more heterogeneous across studies.<sup>192,193,195,197,199,218</sup> Future controlled studies should strive to collect detailed baseline data on the cardiotoxic treatments received by the participants, in a standardized way, so that (1) participants can be stratified based on risk of reduced CPF due to cardiotoxic risk; and (2) samples from different studies can be compared objectively.

Similarly, baseline PA levels should also be a standardized measure as it is also a cardiotoxic risk factor, and is also related to a patient's baseline susceptibility to the indirect effect of cancer and its treatment on CPF. Unfortunately, many of the included studies in this review did not collect data on baseline PA levels. Of the included studies that did collect data on PA levels, these only did so to either monitor whether or not participants were adhering to the prescribed exercise regime during treatment,<sup>195,218</sup> or if they measured PA at baseline, it was to match participants in the different groups,<sup>197</sup> not to judge baseline risk for diminished CPF. If this information was reported in individual studies, it would provide a means of standardizing the effect of an exercise intervention on CPF across studies, rather than considering all studies to have participants with equal susceptibility for diminished CPF. For example, the lack of reported baseline PA levels was an issue for interpreting one finding from the review by Speck et al.,<sup>300</sup> as there was unexplained heterogeneity in the effect of an exercise intervention on fatigue levels across studies. This heterogeneity may have been explained by differences in baseline PA levels had they been reported. Thus, future studies should measure and report baseline PA levels.

It should also be acknowledged that there are certain methodological problems with the comparison of the post-intervention values from the studies included in this review to normative values. One is that in two of the included studies,<sup>192,218</sup> the participants were from countries that are not represented by the available normative data for CPF, since these studies took place outside of North America and Europe (i.e., Taiwan and Israel). Therefore, it should be considered that the differences in broad socio-economic factors in some countries (e.g., affluence of the country, percentage of children and adolescents in a

society, etc.)<sup>301</sup> may translate to lower normative CPF values. Consequently, this may mean less of a discrepancy between the final VO<sub>2</sub> peak values attained in these studies with their true country-specific normative values, which have not been published to date. This possibility is supported by a systematic review and meta-analysis of all studies that reported results on the 20-metre shuttle run test for several populations, spanning several continents. This review found the span of performance between the study/country with the fittest participants and the study/country with the least fit participants could be interpreted as a potential difference in relative VO<sub>2</sub> peak of approximately 10-12 ml/kg/min.<sup>301</sup> Despite this limitation, it is still plausible that CCS are not able to fully recover to the true normative VO<sub>2</sub> peak values of their age-matched counterparts, not even at long-term follow-up.<sup>70,302</sup> However, in order to confirm this, normative values should be determined for all countries in which these studies are conducted.

Lastly, the findings of this review also warrant additional study into which exercise interventions yield the highest adherence levels, and the most beneficial long-term effects (both in behavioural and clinical outcomes), before effective exercise prescription guidelines can be established. Based on the three studies that reported adherence levels in terms of attendance, it is difficult to tell whether or not adherence during the intervention was an issue, as they reported varied findings.<sup>197-199</sup> Moreover, since adherence as measured by attendance is far less meaningful than adherence to exercise prescription parameters, and the latter was not reported by any of the included studies, this further limits the evidence of adherence in this area of research.

As for adoption of lifestyle PA, only three studies reported either behavioural<sup>1</sup> or clinical outcomes<sup>2,3</sup> at long-term follow-up, therefore the long-term effectiveness of an

aerobic exercise intervention could not be investigated adequately. Nonetheless, one of the included studies reported that nine out of ten children in the exercise group reported being more active and had made positive changes in daily exercise behaviours at six month follow-up since the program was completed.<sup>1</sup> Similarly, the two studies that reported follow-up clinical measurements showed that CPF did increase in the exercise groups since the completion of the program.<sup>2,3</sup> Cumulatively, these findings may be indicative of aerobic exercise programs having a lasting effect on lifestyle PA. However, it should be noted that the increase in CPF from the end of the program to the follow-up point was also higher in the control group than the exercise group in both the latter studies, leading to MDs in favour of the control groups. This could be due to control groups adopting an active lifestyle following the study instead of the exercise groups.<sup>198,199</sup> In contrast, a previous study found that the increase in PA levels at follow-up among CCS was higher (albeit not significantly) for the exercise group.<sup>314</sup> Thus, future studies should measure and report standard long-term outcomes (both behavioural and clinical) in order to address this gap in the literature.

In summary, future controlled studies in this area should recruit more participants; ensure reliable CPF measurements; and measure and report cardiotoxic risk factors, specific levels of adherence and both behavioural and clinical outcomes at long-term follow-up. Information on adherence (both during the intervention and in future lifestyle PA) is especially important in CCS, since it has been shown that this population is 20-40% less likely to meet standard guidelines for aerobic exercise<sup>166</sup> than either their siblings<sup>86</sup> or a group of healthy controls.<sup>85</sup>

## Chapter 6: Conclusion

In conclusion, this review suggests that an aerobic exercise intervention elicits a change in CPF in CCS that is both statistically ( $p$ -value  $< 0.05$ ) and clinically significant (MD in relative  $VO_2$  peak  $> 1$  ml/kg/min). Furthermore, the pooled %MD suggests that aerobic exercise may be as effective and efficacious as some proposed pharmacological options for decreased CV mortality rate (e.g., ACE inhibitors, beta-blockers). However, when compared to the results of previous studies in the age-matched healthy population, the pooled effect estimate from this review suggests that the trainability of CPF using aerobic exercise is lower in CCS. Also, based on the comparison of the pooled MD of this review with the pooled MDs of two similar meta-analyses of the adult cancer survivor literature,<sup>76,77</sup> CPF may also be less trainable in CCS than adult cancer survivors.

Unfortunately, none of the subgroup analyses conducted were able to provide any explanation for the moderate heterogeneity of the pooled effect estimate ( $I^2=38\%$ ). It is suspected that this lack of significant findings can be largely attributed to the limited number of studies included in this review, as well as their relatively small, and somewhat heterogeneous sample sizes. Other limitations of the existing literature, particularly the incomplete or absent reporting of relevant information (e.g., adherence, cardiotoxic risk factors, treatment type), precluded the completion of other subgroup analyses.

While the result of this review provides preliminary, conditional support for the effectiveness of aerobic exercise as a cardioprotective strategy for CCS, the main caveats are that the quality of the evidence is low, the outcome measure is not a direct measure of cardioprotection, and there is insufficient evidence to determine which specific exercise parameters are the most effective for which clinical characteristics. Hence, future studies

should strive to attain higher quality grading, larger sample sizes, and implement standardized measurement and reporting procedures. Future trials should also directly compare various exercise parameters (e.g., dose, intensity, modality) in order to determine the relative effectiveness of these interventions. By doing so, these studies will allow future reviews to successfully investigate source(s) of heterogeneity in the effect of aerobic exercise on CPF in CCS; calculate more reliable effect estimates for subgroups; and may eventually inform the development of aerobic exercise guidelines that provide optimal protection against the late cardiotoxic effects of cancer treatment in CCS.

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## Appendix I: Search Strategy for MEDLINE/PubMed

1. For **children**, the following MeSH headings and text words were used:

Infan\* OR newborn\* OR new-born\* OR perinat\* OR neonat\* OR postnat\* OR baby OR baby\* OR babies OR toddler\* OR minors OR minors\* OR boy OR boys OR boyfriend OR boyhood OR girl\* OR kid OR kids OR child OR child\* OR children\* OR schoolchild\* OR schoolchild OR school child[tiab] OR school child\*[tiab] OR adolescen\* OR juvenil\* OR youth\* OR teen\* OR under\*age\* OR pubescen\* OR pediatrics[mh] OR pediatric\* OR paediatric\* OR peadiatric\* OR school[tiab] OR school\*[tiab] OR prematur\* OR preterm\*

2. For **cancer**, the following MeSH headings and text words were used:

neoplasms[mh] OR combined modality therapy[mh] OR antineoplastic agents[mh] OR chemotherapy, adjuvant[mh] OR Radiotherapy, Adjuvant[mh] OR Neoadjuvant Therapy[mh] OR cancer\*[tw] OR oncolog\*[tw] OR neoplas\*[tw] OR tumor\*[tw] OR tumour\*[tw] OR malignan\*[tw] OR carcinom\*[tw] OR bone marrow transplant\*[tw] OR lymphom\*[tw] OR myelom\*[tw] OR adenocarcinom\*[tw] OR leukemi\*[tw] OR leukaemi\*[tw] OR AML[tw] OR lymphom\*[tw] OR hodgkin\*[tw] OR T-cell\*[tw] OR B-cell\*[tw] OR non-hodgkin\*[tw] OR sarcom\*[tw] OR Ewing\*[tw] OR osteosarcom\*[tw] OR wilms[tw] OR nephroblastom\*[tw] OR neuroblastom\*[tw] OR rhabdomyosarcom\*[tw] OR teratom\*[tw] OR hepatom\*[tw] OR hepatoblastom\*[tw] OR PNET\*[tw] OR medulloblastom\*[tw] OR retinoblastom\*[tw] OR meningiom\*[tw] OR gliom\*[tw] OR metastas\*[tw] OR cancer patient\*[tw] OR cancer survivor\*[tw] OR anticancer[tw] OR antineoplastic[tw] OR antitumour[tw] OR antitumor[tw]

3. For **exercise**, the following MeSH headings and text words were used:

sport\*[tw] OR swim\*[tw] OR run\*[tw] OR jog\*[tw] OR ((cycling[tw] OR bike[tw] OR biking[tw])) OR aerobics[tw] OR fitness class\*[tw] OR ((((((house work\*[tw] OR housework\*[tw] OR garden\*[tw] OR walk\*[tw] OR yoga[tw] OR (((("motor activity"[MeSH Terms] OR motor activit\*[tw] OR physical activit\*[tw])) OR (((("Exercise"[Mesh]) OR "Physical Exertion"[Mesh]) OR "Sports"[Mesh]) OR "Exercise Therapy"[Mesh])) OR exercis\*[tw] OR exerciz\*[tw]

4. For **CPF**, the following MeSH headings and text words were used:

Oxygen consumption[mh] OR physical fitness[mh] OR exercise tolerance[mh] AND oxygen consumption[mh] OR respiratory function tests[mh] AND aerobiosis[mh] AND human physical conditioning[mh] OR VO<sub>2</sub>max OR VO<sub>2</sub>peak OR VO<sub>2</sub> OR (VO AND (2peak)) OR peak oxygen consumption OR max oxygen consumption OR maximum oxygen consumption OR oxygen consumption OR physical fitness OR exercise tolerance



OR cardiopulmonary function OR indirect calorimetry OR stress test OR exercise test\*  
OR graded exercise test OR respiratory function test OR gas exchange OR oxygen intake  
OR physical function OR aerobic fitness OR aerobic capacity OR fitness OR physical  
fitness OR physical conditioning\* OR physical effort OR physical activity OR lung  
function OR pulmonary function OR respiratory function OR physical endurance OR  
ventilatory threshold OR endurance OR steep ramp test OR ramp protocol OR  
dynamometer OR Six Minute Walk OR 6MWD OR treadmill OR cycle ergometer OR  
bicycle OR graded exercise test OR walk test OR run test OR walk/run test OR Balke  
protocol OR shuttle run

5. For **RCTs and CCTs**, the following MeSH headings and text words were used:

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR  
placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]  
NOT (animals[mh] NOT humans[mh]))

**Final search:**

1 AND 2 AND 3 AND 4 AND 5

[pt]=publication type

[tiab]=title or abstract

[sh]=subject heading

[mh]=MeSH term

[text]=text word

[\*]=1+ more characters

[RCT]= randomised controlled trial

[CCT]= controlled clinical trial

## Appendix II: Search Strategy for CENTRAL

1. For **children**, the following Emtree terms and text words were used

Infan\* OR newborn\* OR new-born\* OR perinat\* OR neonat\* OR postnat\* OR baby OR baby\* OR babies OR toddler\* OR minors OR minors\* OR boy OR boys OR boyfriend OR boyhood OR girl\* OR kid OR kids OR child OR child\* OR children\* OR schoolchild\* OR schoolchild OR TI school NEXT/1 child OR AB school NEXT/1 child OR TI school NEXT/1 child\* OR AB school NEXT/1 child\* OR adolescen\* OR juvenil\* OR youth\* OR teen\* OR under\* NEXT/1 age\* OR pubescen\* OR pediatrics/exp OR pediatric\* OR paediatric\* OR peadiatric\* OR TI school OR AB school OR TI school\* OR AB school\* OR prematur\* OR preterm\*

2. For **cancer**, the following Emtree terms and text words were used:

'oncology'/exp OR 'oncology' OR 'cancer diagnosis'/exp OR 'cancer diagnosis' OR 'antineoplastic agent'/exp OR 'antineoplastic agent' OR 'cancer chemotherapy'/exp OR 'cancer chemotherapy' OR 'cancer combination' OR 'chemotherapy'/exp OR 'chemotherapy' OR 'cancer hormone therapy'/exp OR 'cancer hormone therapy' OR 'cancer therapy'/exp OR 'cancer therapy' OR 'carcinoma in situ'/exp OR 'carcinoma in situ' OR 'cancer radiotherapy'/exp OR 'cancer radiotherapy' OR 'cancer patient'/exp OR 'cancer patient' OR 'cancer survival'/exp OR 'cancer survival' OR 'adjuvant chemotherapy'/exp OR 'adjuvant chemotherapy' OR 'cancer adjuvant therapy'/exp OR 'cancer adjuvant therapy' OR 'multimodality cancer therapy'/exp OR 'multimodality cancer therapy' OR 'childhood cancer'/exp OR 'childhood cancer' OR 'molecularly targeted therapy'/exp OR 'molecularly targeted therapy' OR 'neoplasm'/exp OR 'neoplasm' OR 'carcinoma'/exp OR 'carcinoma' OR 'tumor'/exp OR 'tumor' OR 'hematooncologic malignancy' OR cancer\* OR oncolog\* OR neoplasm\* OR carcinom\* OR tumor\* OR tumour\* OR malignan\* OR hematooncolog\* OR hemato NEXT/1 oncolog\* OR hematologic NEXT/1 neoplasm\* OR hematolo\* OR leukemi\* OR leukaemi\* OR acute NEXT/1 lymphocytic NEXT/1 leukemia\* OR aml OR lymphoma\* OR hodgkin\* OR 't cell' OR 'b cell' OR non NEXT/1 hodgkin\* OR sarcom\* OR ewing\* OR osteosarcom\* OR wilms NEXT/1 tumor\* OR wilms OR nephroblastom\* OR neuroblastom\* OR rhabdomyosarcoma\* OR teratom\* OR hepatom\* OR hepatoblastom\* OR pnet OR medullablastom\* OR pnet\* OR neuroectodermal NEXT/1 tumor\* OR primitive NEXT/1 neuroectodermal NEXT/1 tumor\* OR retinoblastoma\* OR meningiom\* OR gliom\* OR brain NEXT/1 tumor\* OR brain NEXT/1 tumour\* OR brain NEXT/1 cancer\* OR brain NEXT/1 neoplasm\* OR cns NEXT/1 tumor\* OR cns NEXT/1 tumour\* OR central NEXT/1 nervous NEXT/1 system NEXT/1 tumor\* OR central NEXT/1 nervous NEXT/1 system NEXT/1 tumour\* OR central NEXT/1 nervous NEXT/1 system NEXT/1 neoplasm\* OR cns NEXT/1 neoplasm\* OR intracranial NEXT/1 neoplas\*

3. For **exercise**, the following Emtree terms and text words were used:

'exercise'/exp OR 'aerobic exercise'/exp OR 'resistance exercise'/exp OR 'training'/exp OR 'physical stress'/exp OR 'aerobic work'/exp OR 'energy expenditure'/exp OR 'kinesiotherapy'/exp OR 'physical activity'/exp OR 'pediatric physiotherapy'/exp OR 'physiotherapy'/exp OR 'muscle exercise'/exp OR 'swimming'/exp OR 'locomotion'/exp OR 'treadmill'/exp OR 'treadmill exercise'/exp OR 'walking'/exp OR 'running'/exp OR 'cycling'/exp OR 'jogging'/exp OR 'occupational therapy'/exp OR 'fitness'/exp OR 'weight lifting'/exp OR 'rowing'/exp OR 'sport'/exp OR exercise OR physical NEAR/1 exercise\* OR aerobic NEAR/1 exercise\* OR exercise NEAR/1 therap\* OR physical NEAR/1 therapy NEAR/1 modalit\* OR physiotherap\* OR physical NEAR/1 therap\* OR physical NEAR/1 therapy NEAR/1 technique\* OR training OR exercise NEAR/1 movement NEAR/1 technic\* OR exercise NEAR/1 movement NEAR/1 technique\* OR muscle NEAR/1 train\* OR gymnastic\* OR swim\* OR swimming OR locomotion\* OR treadmill\* OR treadmill NEAR/1 exercise\* OR walking OR walk\* OR running OR run\* OR cycl\* OR jogging OR jog\* OR aerobic\* OR exertion OR exert\* OR occupational NEAR/1 therap\* OR functional NEAR/1 therap\* OR training NEAR/1 program\* OR (physical education and training) OR fitness OR weight NEAR/1 lift\* OR cardio NEAR/1 train\* OR row\* OR rowing OR sport\*

4. For **CPF**, the following Emtree terms and text words were used:

'Cardiopulmonary function'/exp OR 'gas exchange'/exp OR 'oxygen consumption'/exp OR 'cardiovascular function'/exp OR 'fitness'/exp OR 'physical capacity'/exp OR 'aerobic capacity'/exp OR 'exercise test'/exp OR 'oxygen transport'/exp OR 'functional status'/exp OR 'oxygen concentration'/exp OR 'lung function'/exp OR 'cardiovascular effect'/exp OR 'endurance'/exp OR 'Steep Ramp Test'/exp OR Exercise NEXT/1 test\* OR condition\* OR physical fitness OR human NEXT/1 physical NEXT/1 conditioning\* OR physical effort OR lung function OR pulmonary function OR physical endurance OR VO2 OR VO2peak OR VO NEXT/1 2peak OR ventilator threshold OR endurance OR Wingate aerobic test OR steep ramp test OR 6MWD OR Six Minute Walk Distance OR incremental shuttle walking

5. For **RCTs and CCTs**, the following Emtree terms and text words were used:

random\* OR factorial\* OR assign\* OR allocate\* OR ti AND randomized OR ab AND randomized OR ti AND placebo OR ab AND placebo OR ti AND randomly OR ab AND randomly OR ti AND trial OR ab AND trial OR ti AND groups OR ab AND groups OR 'crossover-procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp OR 'controlled clinical trial'/exp OR 'human'/exp

## **Final search**

1 AND 2 AND 3 AND 4 AND 5

[NEAR/1] = requests terms that are within 1 words of each other in either direction

[NEXT/1] = requests terms that are within 1 words of each other in the order specified

[/exp] = explosion

[\*] = 1+ more characters

[ti] = article title

## Appendix III: Search Strategy for EMBASE/Ovid

1. For **children**, the following text words were used for searching Title, Abstract, or Keywords:

Infan\* or newborn\* or new-born\* or perinat\* or neonat\* or postnat\* or baby or baby\* or babies or toddler\* or minors or minors\* or boy or boys or boyfriend or boyhood or girl\* or kid or kids or child or child\* or children\* or schoolchild\* or schoolchild or school child or school child\* or adolescen\* or juvenil\* or youth\* or teen\* or under\*age\* or pubescen\* or pediatrics or pediatric\* or paediatric\* or peadiatric\* or school or school\* or prematur\* or preterm\*

2. For **cancer**, the following text words were used for searching Title, Abstract, or Keywords:

neoplasms or combined modality therapy or antineoplastic agents or chemotherapy, adjuvant or Radiotherapy, Adjuvant or Neoadjuvant Therapy or cancer\* or oncolog\* or neoplas\* or tumor\* or tumour\* or malignan\* or carcinom\* or bone marrow transplant\* or lymphom\* or myelom\* or adenocarcinom\* or leukemi\* or leukaemi\* or AML or lymphom\* or hodgkin\* or Tcell\* or Bcell\* or nonhodgkin\* or sarcom\* or Ewing\* or osteosarcom\* or wilms or nephroblastom\* or neuroblastom\* or rhabdomyosarcom\* or teratom\* or hepatom\* or hepatoblastom\* or PNET\* or medulloblastom\* or retinoblastom\* or meningiom\* or gliom\* or metastas\* or cancer patient\* or cancer survivor\* or anticancer or antineoplastic or antitumour or antitumor

3. For **exercise**, the following text words were used for searching Title, Abstract, or Keywords:

sport\* or swim\* or run\* or jog\* or (cycling or bike or biking) or aerobics or fitness class\* or house work\* or housework\* or garden\* or walk\* or yoga or "motor activity" or motor activit\* or physical activit\* or "Exercise" or "Physical Exertion" or "Sports" or "Exercise Therapy" or exercis\* or exerciz\*

4. For **CPF**, the following text words were used for searching Title, Abstract, or Keywords:

Oxygen consumption OR physical fitness OR exercise tolerance OR oxygen consumption OR respiratory function tests OR aerobiosis OR human physical conditioning OR VO2max OR VO2peak OR VO2 OR (VO AND 2peak) OR peak oxygen consumption OR max oxygen consumption OR maximum oxygen consumption OR oxygen consumption OR physical fitness OR exercise tolerance OR cardiopulmonary function OR indirect calorimetry OR stress test OR exercise test\* OR graded exercise test OR respiratory function test OR gas exchange OR oxygen intake OR physical function OR

aerobic fitness OR aerobic capacity OR fitness OR physical fitness OR physical conditioning\* OR physical effort OR physical activity OR lung function OR pulmonary function OR respiratory function OR physical endurance OR ventilatory threshold OR endurance OR steep ramp test OR ramp protocol OR dynamometer OR Six Minute Walk OR 6MWD OR treadmill OR cycle ergometer OR bicycle OR graded exercise test OR walk test OR run test OR walk NEXT/1 run test OR Balke protocol OR shuttle run

5. For **RCTs and CCTs**, the following text words were used for searching Title, Abstract, or Keywords:

(randomized controlled trial or controlled clinical trial or randomized or placebo or drug therapy or randomly or trial or groups) not (animals not humans)

**Final Search:**

1 AND 2 AND 3 AND 4 AND 5

[\*]=1+ more characters

## Appendix IV: Search Strategy for Web of Science – Core Collection

1. For **children**, the following text words were used:

Infan\* or newborn\* or new-born\* or baby\* or babies or toddler\* or minors\* or boy or boys or boyfriend or boyhood or girl\* or kid or kids or child\* or children\* or schoolchild\* or "school child\*" or adolescen\* or juvenil\* or youth\* or teen\* or under\*age\* or pubescen\* or pediatrics or pediatric\* or paediatric\* or peadiatric\* or school\*

2. For **cancer**, the following text words were used:

neoplasms or "combined modality therapy" or "antineoplastic agents" or "chemotherapy, adjuvant" or "Radiotherapy, Adjuvant" or "Neoadjuvant Therapy" or cancer\* or oncolog\* or neoplas\* or tumor\* or tumour\* or malignan\* or carcinom\* or "bone marrow transplant\*" or lymphom\* or myelom\* or adenocarcinom\* or leukemi\* or leukaemi\* or AML or lymphom\* or hodgkin\* or Tcell\* or Bcell\* or nonhodgkin\* or sarcom\* or Ewing\* or osteosarcom\* or wilms or nephroblastom\* or neuroblastom\* or rhabdomyosarcom\* or teratom\* or hepatom\* or hepatoblastom\* or PNET\* or medulloblastom\* or retinoblastom\* or meningiom\* or gliom\* or metastas\* or cancer patient\* or cancer survivor\* or anticancer or antineoplastic or antitumour or antitumor

3. For **exercise**, the following text words were used:

sport\* or swim\* or run\* or jog\* or (cycling or bike or biking) or aerobics or "fitness class\*" or "house work\*" or housework\* or garden\* or walk\* or yoga or "motor activity" or "motor activit\*" or "physical activit\*" or "Exercise" or "Physical Exertion" or "Sports" or "Exercise Therapy" or exercis\* or exerciz\*

4. For **CPF**, the following text words were used:

"Oxygen consumption" or "physical fitness" or "exercise tolerance" or "oxygen consumption" or "respiratory function tests" or aerobiosis or "human physical conditioning" or VO<sub>2</sub>max or VO<sub>2</sub>peak or VO<sub>2</sub> or (VO and 2peak) or "peak oxygen consumption" or "max oxygen consumption" or "maximum oxygen consumption" or "oxygen consumption" or "physical fitness" or "exercise tolerance" or "cardiopulmonary function" or "indirect calorimetry" or "stress test" or "exercise test\*" or "graded exercise test" or "respiratory function test" or "gas exchange" or "oxygen intake" or "physical function" or "aerobic fitness" or "aerobic capacity" or fitness or "physical fitness" or "physical conditioning\*" or "physical effort" or "lung function" or "pulmonary function" or "respiratory function" or "physical endurance" or "ventilatory threshold" or endurance or "steep ramp test" or "ramp protocol" or dynamometer or "Six Minute Walk" or 6MWD

or treadmill or "cycle ergometer" or bicycle or "graded exercise test" or "walk test" or "run test" or "walk pre/1 run test" or "Balke protocol" or "shuttle run"

5. For **RCTs and CCTs**, the following text words were used:

("randomized controlled trial" or "controlled clinical trial" or randomized or placebo or "drug therapy" or randomly or trial or groups) not (animals not humans)

**Final Search:**

1 AND 2 AND 3 AND 4 AND 5

[\*]=1+ more characters



## Appendix V: Search Strategy for CINAHL

1. For **children**, the following MeSH headings (MH) and text words were used:

(MH "Pediatrics") OR Infan\* or newborn\* or newborn\* or perinat\* or neonat\* or postnat\* or baby or baby\* or babies or toddler\* or minors or minors\* or boy or boys or boyfriend or boyhood or girl\* or kid or kids or child or child\* or children\* or schoolchild\* or schoolchild or TI school child or AB school child or TI school child\* or AB school child\* or adolescen\* or juvenil\* or youth\* or teen\* or under\*age\* or pubescen\* or pediatrics or pediatric\* or paediatric\* or peadiatric\* or TI school or AB school or TI school\* or AB school\* or prematur\* or preterm\*

2. For **cancer**, the following MeSH headings (MH) and text words were used:

(MH "Combined Modality Therapy") OR (MH "Neoadjuvant Therapy") OR (MH "Antineoplastic Agents, Combined") OR (MH "Neoplasms") OR (MH "Antineoplastic Agents") OR (MH "Antineoplastic Agents, Alkylating") OR (MH "Antimetabolites, Antineoplastic") OR (MH "Chemotherapy, Adjuvant") OR (MH "Radiotherapy, Adjuvant") OR (MH "Chemotherapy, Cancer") OR (MH "Cancer Patients") OR (MH "Cancer Survivors") OR (MH "Childhood Neoplasms") OR neoplasms or combined modality therapy or antineoplastic agents or chemotherapy, adjuvant or Radiotherapy, Adjuvant or Neoadjuvant Therapy or cancer\* or oncolog\* or neoplas\* or tumor\* or tumour\* or malignan\* or carcinom\* or bone marrow transplant\* or lymphom\* or myelom\* or adenocarcinom\* or leukemia\* or leukaemi\* or AML or lymphom\* or hodgkin\* or Tcell\* or Bcell\* or nonhodgkin\* or sarcom\* or Ewing\* or osteosarcom\* or wilms or neuroblastom\* or neuroblastom\* or rhabdomyosarcom\* or teratom\* or hepatom\* or hepatoblastom\* or PNET\* or medulloblastom\* or retinoblastom\* or meningiom\* or gliom\* or metastas\* or cancer patient\* or cancer survivor\* or anticancer or antineoplastic or antitumour or antitumor

3. For **exercise**, the following MeSH headings (MH) and text words were used:

(MH "Motor Activity") OR (MH "Physical Activity") OR (MH "Exercise") OR (MH "Aerobic Exercises") OR (MH "Exertion") OR (MH "Pediatric Physical Therapy") OR (MH "Sports") OR (MH "Therapeutic Exercise") OR sport\* or swim\* or run\* or jog\* or (cycling or bike or biking) or aerobics or fitness class\* or house work\* or housework\* or garden\* or walk\* or yoga or "motor activity" or motor activit\* or physical activit\* or "Exercise" or "Physical Exertion" or "Sports" or "Exercise Therapy" or exercis\* or exerciz\*

4. For **CPF**, the following MeSH headings (MH) and text words were used:

(MH "Oxygen Consumption") OR (MH "Physical Fitness") OR (MH "Exercise Tolerance") OR (MH "Exercise Test, Cardiopulmonary") OR Oxygen consumption or physical fitness or exercise tolerance or oxygen consumption or respiratory function tests or aerobiosis or human physical conditioning or VO<sub>2</sub>max or VO<sub>2</sub>peak or VO<sub>2</sub> or (VO<sub>2</sub> and 2peak) or peak oxygen consumption or max oxygen consumption or maximum oxygen consumption or oxygen consumption or physical fitness or exercise tolerance or cardiopulmonary function or indirect calorimetry or stress test or exercise test\* or graded exercise test or respiratory function test or gas exchange or oxygen intake or physical function or aerobic fitness or aerobic capacity or fitness or physical fitness or physical conditioning\* or physical effort or physical activity or lung function or pulmonary function or respiratory function or physical endurance or ventilatory threshold or endurance or steep ramp test or ramp protocol or dynamometer or Six Minute Walk or 6MWD or treadmill or cycle ergometer or bicycle or graded exercise test or walk test or run test or walk W1 run test or Balke protocol or shuttle run

5. For **RCTs and CCTs**, the following text words were used:

(randomized controlled trial or controlled clinical trial or randomized or placebo or drug therapy or randomly or trial or groups) not (animals not humans)

**Final Search:**

1 AND 2 AND 3 AND 4 AND 5

[MH] = MeSH headings: exploding retrieves all documents containing any of the subject terms below the term selected.

[RCT]= randomised controlled trial

[CCT]= controlled clinical trial

[\*]=1+ more characters

## Appendix VI: Search Strategy for SPORTDiscus

1. For **children**, the following text words were used:

Infan\* or newborn\* or newborn\* or perinat\* or neonat\* or postnat\* or baby or baby\* or babies or toddler\* or minors or minors\* or boy or boys or boyfriend or boyhood or girl\* or kid or kids or child or child\* or children\* or schoolchild\* or schoolchild or school child or school child\* or adolescen\* or juvenil\* or youth\* or teen\* or under\*age\* or pubescen\* or pediatrics or pediatric\* or paediatric\* or peadiatric\* or school or school\* or prematur\* or preterm\*

2. For **cancer**, the following text words were used:

neoplasms or combined modality therapy or antineoplastic agents or chemotherapy, adjuvant or Radiotherapy, Adjuvant or Neoadjuvant Therapy or cancer\* or oncolog\* or neoplas\* or tumor\* or tumour\* or malignan\* or carcinom\* or bone marrow transplant\* or lymphom\* or myelom\* or adenocarcinom\* or leukemia\* or leukaemi\* or AML or lymphom\* or hodgkin\* or Tcell\* or Bcell\* or nonhodgkin\* or sarcom\* or Ewing\* or osteosarcom\* or wilms or nephroblastom\* or neuroblastom\* or rhabdomyosarcom\* or teratom\* or hepatom\* or hepatoblastom\* or PNET\* or medulloblastom\* or retinoblastom\* or meningiom\* or gliom\* or metastas\* or cancer patient\* or cancer survivor\* or anticancer or antineoplastic or antitumour or antitumor

3. For **exercise**, the following text words were used:

sport\* or swim\* or run\* or jog\* or (cycling or bike or biking) or aerobics or fitness class\* or house work\* or housework\* or garden\* or walk\* or yoga or "motor activity" or motor activit\* or physical activit\* or "Exercise" or "Physical Exertion" or "Sports" or "Exercise Therapy" or exercis\* or exerciz\* )

4. For **CPF**, the following text words were used:

Oxygen consumption or physical fitness or exercise tolerance or oxygen consumption or respiratory function tests or aerobiosis or human physical conditioning or VO<sub>2</sub>max or VO<sub>2</sub>peak or VO<sub>2</sub> or (VO and 2peak) or peak oxygen consumption or max oxygen consumption or maximum oxygen consumption or oxygen consumption or physical fitness or exercise tolerance or cardiopulmonary function or indirect calorimetry or stress test or exercise test\* or graded exercise test or respiratory function test or gas exchange or oxygen intake or physical function or aerobic fitness or aerobic capacity or fitness or physical fitness or physical conditioning\* or physical effort or physical activity or lung function or pulmonary function or respiratory function or physical endurance or ventilatory threshold or endurance or steep ramp test or ramp protocol or dynamometer or

Six Minute Walk or 6MWD or treadmill or cycle ergometer or bicycle or graded exercise test or walk test or run test or walk W1 run test or Balke protocol or shuttle run

5. For **RCTs and CCTs**, the following text words were used:

(randomized controlled trial or controlled clinical trial or randomized or placebo or drug therapy or randomly or trial or groups) not (animals not humans)

**Final Search:**

1 AND 2 AND 3 AND 4 AND 5

[\*]=1+ more characters

## Appendix VII: Search Strategy for ProQuest Digital Dissertations

all(cancer or neoplasms or oncology) AND (physical activity OR exercise or exercise therapy) AND (child OR pediatric) AND (cardiopulmonary fitness or oxygen consumption OR exercise tolerance)

## Appendix VIII: Search Strategy for PEDro

Combination #1: cancer physical activity

Combination #2: cancer exercise

## Appendix IX: Search Terms and Search Strategies for Grey Literature Sources and Hand-searching

Source	Terms used to search (and search strategy details)
<b>Grey literature sources</b>	
American Institute for Cancer Research	Searched the results of a suggested PubMed search strategy that appeared as a link after I googled "american institute for cancer research conference proceedings" (searched the first 60 records of these PubMed results); Google advanced searched web page ( <a href="http://www.aicr.org/">http://www.aicr.org/</a> ): "exercise cardiorespiratory", and "exercise child" (searched in <u>all these words</u> , while also narrowing for only English results); searched "exercise", "physical", "activity", "children" in Conference archives at <a href="http://www.aicr.org/cancer-research/conference/#program-and-posters.html">http://www.aicr.org/cancer-research/conference/#program-and-posters.html</a> (searched 4 available conference programs: years 2010, 2011, 2013, and 2014)
American Cancer Society	Could not find the conference abstracts/proceedings page; Google advanced searched: "exercise cardiorespiratory", "exercise child"(searched both in <u>all these words</u> , while also narrowing for only English results)
Canadian Cancer Research Conference	Searched "exercise", "physical", "activity", and "children" (the only webpage I was able to find that contained some potential grey literature was an archive page for the past conferences ( <a href="https://www.ccra-acrc.ca/index.php/archive/past-meetings">https://www.ccra-acrc.ca/index.php/archive/past-meetings</a> ); searched each of the three files for the three past meetings).
Danish Cancer Society	Searched "exercise", "physical", "activity", "children" (searched "Scientific Publications" tab for all 5 available years of scientific publications (2011-2015) on Danish Cancer Society, Research Centre web page ( <a href="https://www.cancer.dk/research/publications-research-center/">https://www.cancer.dk/research/publications-research-center/</a> )).
Dutch Cancer Society	<i>Difficult to navigate web page since it is mostly in Dutch.</i> Google advanced searched ( <a href="https://www.kwf.nl/english/pages/default.aspx">https://www.kwf.nl/english/pages/default.aspx</a> ): "exercise cardiorespiratory", "exercise cardiopulmonary", "exercise", "child" (searched both in <u>all these words</u> , while also narrowing for only English results); also google searched "exercise dutch cancer society conference"
German Josep Carreras Leukemia Foundation	Could not find the conference abstracts/proceedings page; Google advanced searched ( <a href="http://www.fcarreras.org/en">http://www.fcarreras.org/en</a> ): "exercise cardiorespiratory", "exercise cardiopulmonary", "exercise", "exercise child", "exercise childhood", "exercise pediatric" (searched both in <u>all these words</u> , while also narrowing for only English results)
National Cancer Institute, Division of Cancer Control & Population Studies, Resources & Information, For Researchers	Preliminary screen of web page ( <a href="http://cancercontrol.cancer.gov/ocs/resources/researchers.html">http://cancercontrol.cancer.gov/ocs/resources/researchers.html</a> ); Searched "exercise", "physical", "activity", "children", and "pediatric" in "Past Biennial Cancer Survivorship Research Conferences" (searched "agendas", as well as "conference highlights and presentation" for 2004, 2006, 2008, 2010, 2012, 2014).

Source	Terms used to search (and search strategy details)
<b>Grey literature sources</b>	
WHO ICTRP	"cancer AND exercise" in title field; "cancer and physical activity" in title field; "cancer AND aerobic" in title field (recruitment status is "ALL" and "clinical trials in children" is activated)
Google Scholar	Searched "exercise cardiorespiratory cancer intervention child 'childhood cancer' "
<b>Hand-Searching</b>	
World Journal of Meta-Analysis	Google advanced searched ( <a href="http://www.wjgnet.com/2308-3840/">http://www.wjgnet.com/2308-3840/</a> ) using "exercise cancer" (searched in <u>all these words</u> , while also narrowing for only English results)



## Appendix X: Inclusion Assessment Form Screening Criteria

The following is a list of the criteria included in the screening assessment form. Please refer to **Appendix XI** for an explanation of how this form was used.

1. Report ID
2. Study ID
3. Date screened
4. English language report?
5. VO<sub>2</sub> max and/or VO<sub>2</sub> peak and/or submaximal test result that can be used to predict either VO<sub>2</sub> peak or VO<sub>2</sub> max reported?
6. Study design (CCT or RCT?) and specify which.
7. One or more intervention groups receiving exercise program?
8. Intervention includes aerobic exercise component?
9. All or some participants are  $\leq 19$  at age of diagnosis?
10. Control group not given any exercise intervention?
11. All or some factors of exercise intervention explicitly stated (i.e., intensity; frequency; time per session; duration of intervention; aerobic exercise type; type of supervision) and specify which ones.
12. VO<sub>2</sub> max and/or VO<sub>2</sub> peak determined via EITHER 1) maximal aerobic protocol (with one of necessary criteria met for VO<sub>2</sub> peak), OR 2) predictive submaximal aerobic protocol (that has been validated for the current age of the cohort being tested)?
13. Participants currently receiving or received cardiotoxic cancer treatment?
14. Include/exclude/unclear?
15. Description (reason for exclusion)
16. Independently assessed and compared?
17. Third author comparison (if necessary)
18. Final verdict?
19. Further details requested? Final verdict?
20. Contact details of authors

## Appendix XI: Instruction Sheet for Inclusion Assessment Form

**Before starting to screen full-text reports using the study inclusion form, all reports that were deemed potentially eligible (PE) based on their title and abstract were reviewed to identify identical reports, or potentially duplicate publications. This was done using the following criteria (according to the Cochrane Handbook for Systematic Reviews of Interventions):**

- *author names (most duplicate reports have authors in common, although it is not always the case);*
- *location and setting (particularly if institutions, such as hospitals, are named);*
- *specific details of the interventions (e.g. dose, frequency);*
- *numbers of participants and baseline data; and*
- *date and duration of the study (which can also clarify whether different sample sizes are due to different periods of recruitment).*

*Where uncertainties remain after considering these and other factors, it may be necessary to correspond with the authors of the reports.*

**Once this step has been completed, the inclusion assessment form is to be used as follows:**

1. Input all report IDs, and study IDs (in case of **duplicate publication** from the same study) for all reports and studies, respectively. Before allocating a study ID, it will be essential to link multiple reports of the same study, whether they are duplicates (i.e., the same paper) or duplicate publications (i.e., multiple papers for the same study). This is prompted by the note at the top of the column B (i.e., “STOP, REMEMBER TO LINK MULTIPLE REPORTS OF THE SAME STUDY BEFORE PROCEEDING!”)
2. To begin completing the study inclusion form, take the report corresponding to the report ID and study ID in cells A2 and C2, respectively, and begin completing row 2 of the table, from left to right. Use a new row for each new subsequent report, always remembering to match the report by report ID and study ID before beginning.
3. Begin with the “**date screened**” column by entering today’s date.
4. Work your way across the inclusion assessment form, filling in each column with one of the indicated response options (e.g., for most columns *yes*, *no*, and *unclear* are the response options). Please work your way across the inclusion assessment form from left to right, as the columns (i.e., eligibility criteria) have been organized in order of importance, as well as screening efficacy.
5. The response options that are written in **red** are those that constitute exclusion from the review, if they are selected.
6. **NOTE:** If *unclear* is selected as a response in any of the columns, it may be necessary to 1) discuss this with the other reviewers before reaching a final verdict for this report (i.e., included or excluded), and 2) possibly contact the author(s) of the report. However, this action will only be taken if none of the other responses already constitute exclusion.
7. **NOTE:** The column titled “**All or some participants are ≤19 at age of diagnosis?**” may require special consideration. Specifically, if the response option **some** is indicated, it

will be necessary to determine whether the results for the participants that meet this criteria are reported separately. If they are not, a judgement will have to be made as to whether it is worthwhile to contact the author(s) to retrieve these results. This judgement should be done in consultation with the other reviewers. However, if the results for the participants that meet this criteria are not reported separately, and it is deemed not worthwhile to contact the author(s) of the report, this report will be excluded from the review.

8. **NOTE:** For the column titled “**VO2 max and/or VO2 peak determined via EITHER 1) maximal aerobic protocol (with one of necessary criteria met for VO2 peak), OR 2) predictive submaximal aerobic protocol (that has been validated for the current age of the cohort being tested)?**” some additional information may be needed to reach a judgement. Specifically, the *necessary criteria met for VO2 peak* are at least one of the following (measured concurrently with VO2 peak): 1) a HR<sub>max</sub> of within  $\pm 10$  beats of the age-predicted HR<sub>max</sub> (i.e.,  $220 - \text{age}$ ); 2) a respiratory exchange ratio  $>1.10$ ; and/or 3) a blood lactate value  $>8$  mmol/L. As for the criterion for the predictive submaximal aerobic protocol (i.e., *validated for the current age of the cohort being tested*), this should be directly referenced in the report. If no validation study is referenced in the report, it may be necessary to research this independently, and then reach a judgement in consultation with the other reviewers.
9. Once you reach the column titled “**Include/exclude/unclear**”, please only indicate **include** if you did not select any of the **red** response options, nor any of the *unclear* response option, in any of the previous columns. If you selected a **red** response option in one or more of the previous columns, please indicate **exclude**. If you selected *unclear* in one or more of the previous columns (and did not select a **red** response option in any of the previous columns) please indicate **unclear**.
10. IF you indicated **include**, the only columns you must complete out of the remaining columns on the inclusion assessment form are the columns titled “**Independently assessed and compared?**” and “**Final verdict?**”. This will be completed once you have met with the other reviewers to reach a final verdict on this report.
11. IF you indicated **exclude**, please provide a brief explanation as to why, in the column titled “**Description (reason for exclusion)**”.
12. IF you indicated **unclear**, please complete the column titled “**Independently assessed and compared?**” once you have met with the other reviewers to reach a final verdict on this report.
13. IF you indicated **unclear**, please complete the column titled “**Final verdict?**” once you have met with the other reviewers to reach a final verdict on this report.
14. IF a final verdict is still not reached after you have met with the other reviewers, author(s) of the report will need to be contacted. Once the report author(s) have been contacted, complete the inclusion assessment form by filling out the remaining columns (i.e., “**Further details requested? Final verdict?**” and “**Contact details of authors**”).

Appendix XII: Table of Included Studies (Study ID), their Associated Reports (Citation(s)), and the Search Strategy or Strategies that Led to their Identification and Inclusion (Search Strategy)

Study ID	Citation(s)	Search Strategy
Dubnov-Raz 2015	Dubnov-Raz, G., Azar, M., Reuveny, R., Katz, U., Weintraub, M., & Constantini, N. W. (2015). Changes in fitness are associated with changes in body composition and bone health in children after cancer. <i>Acta Paediatrica</i> . <sup>192</sup>	Electronic database search
Shore 1999	(1) Shore, S. (1998). The effect of a moderate aerobic training program on T, B, and natural killer cell number and function in normal adults, normal children, and children with cancer. (dissertation); <sup>193</sup> (2) Shore, S., & Shepard, R. J. (1999). Immune responses to exercise in children treated for cancer. <i>Journal of sports medicine and physical fitness</i> , 39(3), 240. <sup>221</sup>	Electronic database search
Braam 2010	(1) Katja Braam, MSc, e-mail communication, January 2016; (2) Braam, K. I., van Dijk, E. M., Veening, M. A., Bierings, M. B., Merks, J. H., Grootenhuis, M. A., ... & Kaspers, G. J. (2010). Design of the Quality of Life in Motion (QLIM) study: a randomized controlled trial to evaluate the effectiveness and cost-effectiveness of a combined physical exercise and psychosocial training program to improve physical fitness in children with cancer. <i>BMC cancer</i> , 10(1), 624; <sup>198</sup> (3) Dijk-Lokkart, E. M., et al. (2015). Effects of a combined physical and psychosocial intervention program for childhood cancer patients on quality of life and psychosocial functioning: results of the QLIM randomized clinical trial. <i>Psycho-Oncology</i> . <sup>220</sup>	Contact with First Author (following electronic database search)
Soares-Miranda 2013	(1) Alejandro Lucia Mulas, MD, PhD, e-mail communication, January 2016; (2) Soares-Miranda, L., Fiuza-Luces, C., Lassaletta, A., Santana-Sosa, E., Padilla, J. R., Fernández-Casanova, L., ... & Lucia, A. (2013). Physical Activity in Pediatric Cancer patients with solid tumors (PAPEC): Trial rationale and design. <i>Contemporary clinical trials</i> , 36(1), 106-115. <sup>199</sup>	Contact with First Author (following electronic database search)
Marchese 2003	(1) Gocha, V. A., Chiarello, L. A., & Lange, B. J. (2002). Physical therapy intervention for children with acute lymphoblastic leukemia. (dissertation); <sup>219</sup> (2) Marchese, V. G., Chiarello, L. A., & Lange, B. J. (2004). Effects of physical therapy intervention for children with acute lymphoblastic leukemia. <i>Pediatric blood &amp; cancer</i> , 42(2), 127-133. <sup>194</sup>	Electronic database search

Study ID	Citation(s)	Search Strategy
Moyer-Mileur 2009	Moyer-Mileur, L. J., Ransdell, L., & Bruggers, C. S. (2009). Fitness of children with standard-risk acute lymphoblastic leukemia during maintenance therapy: response to a home-based exercise and nutrition program. <i>Journal of pediatric hematology/oncology</i> , 31(4), 259-266. <sup>195</sup>	Electronic database
Tanir 2012	Tanir, M. K., & Kuguoglu, S. (2013). Impact of exercise on lower activity levels in children with acute lymphoblastic leukemia: a randomized controlled trial from Turkey. <i>Rehabilitation nursing</i> , 38(1), 48-59. <sup>196</sup>	Electronic database
Chiang 2007	(1) Yi-Chien Chang, PhD RN, e-mail communication, February 2016; (2) Chiang, Y. C. (2007). The effects of “a home-based aerobic exercise intervention” on fatigue and cardiorespiratory fitness in children with acute lymphoblastic leukemia during the maintenance stage of chemotherapy. Chang Gung University, Tao-Yuan, Taiwan (Unpublished doctoral thesis); <sup>218</sup> (3) Yeh, C. H., Wai, J. P. M., Lin, U. S., & Chiang, Y. C. (2011). A pilot study to examine the feasibility and effects of a home-based aerobic program on reducing fatigue in children with acute lymphoblastic leukemia. <i>Cancer nursing</i> , 34(1), 3-12. <sup>222</sup>	Contact with First Author (following reference list searching)
Niesen-Vertommen 1998	Niesen-Vertommen, S. (1998). The recovery patterns and effects of exercise rehabilitation on the physiological and psychological health of children who have survived treatment for a malignancy (T). Retrieved from <a href="https://open.library.ubc.ca/cIRcle/collections/831/items/1.0076930">https://open.library.ubc.ca/cIRcle/collections/831/items/1.0076930</a> (dissertation) <sup>197</sup>	Electronic database

Appendix XIII: A Specific Description of How Many Records were Retrieved vs. How Many Records were Screened

Source	# of citations retrieved	# of records screened	Details
<b>Grey literature sources</b>			
American Institute for Cancer Research	461	116	Only screened the first 60 records within the PubMed search strategy results (which were discovered in the Google search results for “American Institute for Cancer Research conference proceedings”) and stopped because no PE records were found; also screened all 8 records from the “exercise cardiorespiratory” Google advanced search, and all 48 records from the “exercise child” Google advanced search; also screened 4 available conference programs but did not record number of citations retrieved for each program using iterative Google Chrome “find” key word searching ( <b>6 PE records</b> )
American Cancer Society	967	114	Only screened the first 100 records for the “exercise child” Google advanced search and stopped because no PE records were found
Canadian Cancer Research Conference	Not recorded	Not recorded	Screened 3 available files for past meetings but did not record number of citations retrieved for each using Google Chrome “find” key word searching (all results were of peripheral interest)
Danish Cancer Society	Not recorded	Not recorded	Screened 5 available years of scientific publications (under “Scientific Publications” tab), but did not record number of citations retrieved for each using Google Chrome “find” key word searching (all results were of peripheral interest)

Source	# of citations retrieved	# of records screened	Source
<b>Grey literature sources</b>			
Dutch Cancer Society	0 (+ Google search results)	60	Only screened the first 60 records from the Google search results for “exercise Dutch Cancer Society Conference” and stopped because no PE records were found
German Josep Carreras Leukemia Foundation	1042	102	Only screened the first 100 records from the “exercise” Google advanced search and stopped because no PE records were found
National Cancer Institute, Division of Cancer Control & Population Studies, Resources & Information, For Researchers	Not recorded	Not recorded	Screened 6 available years of past research conference proceedings (under “Past Biennial Cancer Survivorship Research Conferences” tab), but did not record number of citations retrieved for each using Google Chrome “find” key word searching ( <b>2 PE records were found</b> )
WHO ICTRP	27	27	<b>2 PE records</b>
Google Scholar	3580	60	Only screened the first 60 records from this search and stopped because only <b>1 PE record was found</b>
<b>TOTAL:</b>	<b>6,077+</b>	<b>479+</b>	Both values are underestimations because the # of citations retrieved and the # of records screened from some of the grey literature sources, when using Google Chrome “find” key word searching, were not recorded; also the # of citations retrieved using the Google search for the Dutch Cancer Society were not included in the total (i.e., 812, 000 search results)
<b>Other sources</b>			
“cited reference” searching	515	515	Used the included studies to perform this search
PubMed “Similar articles” function	970	676	For the “Similar articles” search for four articles, more than 100 citations were retrieved, and in these cases, only 100 records were screened

## Appendix XIV: Characteristics of Dubnov-Raz 2015

Methods	Design: CCT Setting: Israel Randomisation: not performed Stratification: none Study Duration: not reported Treatment Status: 100% off-treatment Measurement Time Points: baseline and post-intervention
Participants	n= 21 Diagnosis: 36% ALL; 14% BL; 9% HL; 41% other Age at start of study: median age (IQR) of intervention group was 11.1 (7.8-13.8), and median age (IQR) of control group was 11.8 (9.0-12.8) Gender ratio (male:female): 4:6 in intervention group, and 6:6 in control group
Intervention	Intensity: Moderate; Frequency: 3/week; Time per session: 55-60 minutes (including warm-up and cool-down); Duration: 6 months; Aerobic exercise type: Unclear (potentially games or exercise machines)
Outcomes	<b>CPF:</b> Godfrey protocol, outcome is relative VO2 peak <b>Secondary Outcomes:</b> body composition, and mental health

### *Risk of Bias*

Bias	Author's judgement	Description
Sequence generation (selection bias)	High Risk	No randomization; allocation by preference of the participant and/or availability of the intervention
Allocation concealment (selection bias)	High Risk	There was no allocation concealment, since intervention was allocated based on preference of the participant. Stated in report that "Participants who were interested in performing the exercise programme were referred to designated existing exercise groups near their home."
Blinding of outcome assessors (performance bias) – CPF	Unclear Risk	Not reported whether outcome assessors were blinded to group assignment



### *Risk of Bias*

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Incomplete Outcome Data (attrition bias) – CPF	Low Risk	Only one control participant did not complete the follow-up evaluation (including post-intervention exercise test); therefore, reason for missing outcome data unlikely to be related to true outcome.
Selective Reporting (reporting bias)	Unclear Risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Other forms of bias	High Risk	There is at least one important risk of bias. One potential source of bias (favouring exercise) is that there were different baseline characteristics in terms of the intervention group and the control group having different access to the exercise program/centres, as well as the control group potentially not being inclined to exercise; none of the participants had "known cardiac dysfunction, any chronic disease, chronic medication, self-reported fatigue" – may not be representative of actual childhood cancer survivor population; there was a lack of sample size calculation (for VO <sub>2</sub> peak or otherwise); and, there was no comparison of the differences in excluded participants from included participants.

## Appendix XV: Characteristics of Shore 1998

Methods	Design: CCT (assumed) Setting: Canada Randomisation: nor performed Stratification: none Study Duration: 8 months Treatment Status: 67% on-treatment; 33% off-treatment Measurement Time Points: baseline & post-intervention
Participants	n= 6 Diagnosis: 50% ALL; 17% non-HL; 33% ES Age at start of study: mean age (SD) of intervention group was 14 (1), and mean age (SD) of control group was 13 (5.3) Gender ratio (male:female): 3:0 in intervention group, and 1:2 in control group
Intervention	Intensity: Moderate (70-85% individual max HR); Frequency: 3-4/week; Time per session: 30 minutes (NOT including 5-min warm-up and 5-min cool-down); Duration: 12 weeks; Aerobic exercise type: potentially cycling, soccer, skating, cross-country skiing, swimming, or combination
Outcomes	<b>CPF:</b> Jones protocol, outcome is relative VO <sub>2</sub> peak <b>Secondary Outcomes:</b> body composition, and immune profile

<b><i>Risk of Bias</i></b>		
<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Sequence generation (selection bias)	High Risk	No randomization, as participants began tests and intervention as they were recruited and the experimenters “continued recruiting and testing children until the exercise laboratory was closed down for reasons of funding”
Allocation concealment (selection bias)	Unclear Risk	Unclear whether there was allocation concealment since there was no randomization (i.e., cannot tell how allocation decisions were made, and when the participant would have found out which group it was allocated to)
Blinding of outcome assessors (performance bias) – CPF	Unclear Risk	Not reported whether outcome assessors were blinded to group assignment

### ***Risk of Bias***

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Incomplete Outcome Data (attrition bias) – CPF	Low Risk	One intervention participant was lost due to schedule conflict with chemotherapy; this reason for missing outcome data is unlikely to introduce significant bias/be related to true outcome.
Selective Reporting (reporting bias)	Unclear Risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Other forms of bias	Unclear Risk	There is at least one important risk of bias. A few things may compromise representativeness, although this is unclear for all of them (i.e., insufficient evidence); may have been some baseline imbalances based on cursory examination of the demographic and baseline data of both groups (i.e., height, body mass, gender proportions, baseline VO <sub>2</sub> peak, and baseline max HR); and, it is unclear whether or not the exercise test used in this study has been validated in this age group (14+/- 1 years)

## Appendix XVI: Characteristics of Braam 2010

Methods	<p>Design: RCT</p> <p>Setting: Netherlands</p> <p>Randomisation: After baseline measurements, and after being stratified according to type of malignancy, sex, pubertal stage; otherwise not specified</p> <p>Stratification: stratified according to type of malignancy, sex, pubertal stage, and treatment status</p> <p>Study Duration: 6 years and 5 months</p> <p>Treatment Status: 32% on-treatment; 68% off-treatment</p> <p>Measurement Time Points: baseline, 1 month follow-up, and 9 months follow-up</p>
Participants	<p>n= 68</p> <p>Diagnosis: <i>No exact proportions</i>; minimum 50% hematological, and maximum 50% solid tumour</p> <p>Age at start of study: mean age (SD) of entire sample was 12.8 (3.1) (<i>according to data from 55 participants</i>)</p> <p>Gender ratio (male:female): 16:14 in intervention group, and 20:18 in control group</p>
Intervention	<p>Strategies: 3 phases of one month each. 1st phase is only aiming to perform moderate cardiorespiratory exercise; 2nd phase aims to increase CRF; and 3rd phase somewhat aims to increase CRF. Weeks 6-12, add 5 home exercises, twice/week, accompanied by music. Intensity: gradually increasing (66-77%, 77-90%, &gt;90% HR max); Frequency: 2/week; Time per session: 45 minutes; Duration: 12 weeks; Aerobic exercise type: Not reported; Adherence: two thirds of participants completed all physical training sessions, remaining third completed average of 18/24 training sessions (range = 10-23)</p>
Outcomes	<p><b>CPF:</b> Godfrey protocol, outcome is relative VO<sub>2</sub> peak</p> <p><b>Secondary Outcomes:</b> muscle strength, inactivity-related adverse health problems, and cost-effectiveness</p>

***Risk of Bias***

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Sequence generation (selection bias)	Low Risk	Unclear what exact randomization procedure was, however it occurred after baseline measurements and after being stratified according to diagnosis, sex, pubertal stage, and timing of recruitment (during or shortly after treatment)
Allocation concealment (selection bias)	Unclear Risk	Probably (for participants), since randomization only occurred after baseline measurements and stratification; but it is unclear if this would have concealed the allocation from investigators
Blinding of outcome assessors (performance bias) – CPF	Unclear Risk	Not reported whether outcome assessors were blinded to group assignment
Incomplete Outcome Data (attrition bias) – CPF	High Risk	With subsequent time points of data collection, the size of both the intervention and control group decreases, and there is no reasons given for the missing participants at subsequent time points (and therefore, no reason for their data not being included in the summary means and difference in means); Also, intention-to-treat analysis done with substantial departure of the intervention received from that assigned at randomization (i.e., intention-to-treat analysis done for those who discontinue participation in the intervention group, but complete the follow-up assessments)
Selective Reporting (reporting bias)	Unclear Risk	Not all of the study's pre-specified outcome measures (i.e., those mentioned in the protocol) have been reported/retrieved (this includes data for the secondary outcome measures of interest). However, this is due to the fact that all of the outcome data that was retrieved for this study was received in an e-mail from the primary author. Cannot be sure whether it is the intention of the author(s) to report the data for the other outcomes once they publish findings.

### *Risk of Bias*

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Other forms of bias	Unclear Risk	A few things may compromise representativeness, although this is unclear for all of them (i.e., insufficient evidence); unclear if some parts of the exercise test protocol used in this study may not be validated (i.e., "using the average value over the last 30 seconds" to calculate VO2 peak, and maintaining a certain cycle speed during the test)

## Appendix XVII: Characteristics of Soares-Miranda 2013

Methods	<p>Design: RCT          Setting: Spain          Randomisation: not specified          Stratification: Each participant randomly assigned with blocking on sex          Study Duration: 3 years          Treatment Status: 100% on-treatment          Measurement Time Points: baseline, post-intervention, and 2 months follow-up</p>	
Participants	<p>n= 49          Diagnosis: 12.16% HL; 24.8% non-HL; 14% Soft-tissue sarcoma; 34.9% bone tumour; 14% other          Age at start of study: mean age (SD) of intervention group was 10 (1), and mean age (SD) of control group was 12 (1)          Gender ratio (male:female): 17:7 in intervention group, and 18:7 in control group</p>	
Intervention	<p>Intensity: Moderate (60-70% individual max HR); Frequency: 3/week; Time per session: a conditioning period of 30 min of aerobic exercise, that is gradually increasing in load (+ approximately 30 min of strength training); Duration: variable, minimum of 9 weeks, maximum of 41 weeks;          Aerobic exercise type: potentially cycle-ergometer pedaling, running, aerobic games; Adherence: mean (SD) is 68(4)% for intervention group</p>	
Outcomes	<p><b>CPF:</b> Maximal graded exercise protocol, outcome is relative VO2 peak  <b>Secondary Outcomes:</b> immune profile, “cancer control”, and PA levels</p>	
<b><i>Risk of Bias</i></b>		
<b>Bias</b>	<b>Author’s judgement</b>	<b>Description</b>
Sequence generation (selection bias)	Low Risk	Unclear what exact randomization procedure was, however it is stated that “each participant [was] randomly assigned (with blocking on sex)”

### ***Risk of Bias***

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Allocation concealment (selection bias)	Unclear Risk	Probably (for participants), since baseline measurements conducted before allocation to intervention or control group / at least before beginning intervention; but it is unclear if this would have concealed the allocation from investigators
Blinding of outcome assessors (performance bias) – CPF	Low Risk	Blinding of outcome assessment ensured (i.e., “blinded assessor”); and even if the blinding could have been broken, the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding
Incomplete Outcome Data (attrition bias) – CPF	Unclear Risk	Unclear, since original number of participants allocated was never explicitly stated (but was assumed to be the same as the # included/evaluated) (i.e., Insufficient reporting of attrition/exclusions to permit judgement)
Selective Reporting (reporting bias)	Unclear Risk	Not all of the study’s pre-specified outcome measures (i.e., those mentioned in the protocol) have been reported/retrieved (this includes data for the secondary outcome measures of interest). However, this is due to the fact that all of the outcome data that was retrieved for this study was received in an e-mail from the primary author. Cannot be sure whether it is the intention of the author(s) to report the data for the other outcomes once they publish findings.



### *Risk of Bias*

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Other forms of bias	High Risk	There is at least one important risk of bias. Representativeness may be compromised, although this is unclear (i.e., insufficient evidence); the groups were not comparable in diagnoses, which may have affected 1. The duration of exercise intervention (based on study design), and 2. the levels of baseline MVPA, as these have been shown to be different for different proportions/types of diagnoses by this group; the exercise program/study design may not have been designed to optimize benefit to outcome of CPF (i.e., main rationale is that "studies have shown that moderate regular exercise can improve immune function, and that it may even have an impact on cancer control"); and, the protocol (treadmill version) used in this study, does not have a validation study associated with it (unclear if it is validated)

## Appendix XVIII: Characteristics of Marchese 2003

Methods	<p>Design: RCT</p> <p>Setting: USA</p> <p>Randomisation: use of envelopes selected by children</p> <p>Stratification: Children were stratified by their Children's Cancer Group (CCG) risk group, and whether they were in the 1<sup>st</sup> or 2<sup>nd</sup> half of maintenance therapy</p> <p>Study Duration: not reported</p> <p>Treatment Status: 100% on-treatment</p> <p>Measurement Time Points: baseline and post-intervention</p>
Participants	<p>n= 28</p> <p>Diagnosis: 100% ALL</p> <p>Age at start of study: mean age (SD) of entire sample was 8.1 (2.5), mean age of intervention group was 8.6, and mean age of control group was 7.6</p> <p>Gender ratio (male:female): 8:5 in intervention group, and 12:3 in control group</p>
Intervention	<p>Intensity: HR-guided; variable based on observation by therapist of child performing an aerobic activity while monitoring HR, breathing rate, and work of breathing;</p> <p>Frequency: Aerobic fitness component was daily ("depends on how long the person walks each time" based on Winningham, 1991, modification for pediatric population); Time per session: 5-45 mins based on observation by therapist of child performing an aerobic activity while monitoring HR, breathing rate, and work of breathing (based on Winningham, 1991, modification for pediatric population); Duration: 4 months; Aerobic exercise type: potentially walking, biking, or swimming (selected by children for themselves)</p>
Outcomes	<p><b>CPF:</b> 9-minute-run-walk test, outcome is distance (metres)</p> <p><b>Secondary Outcomes:</b> muscle strength, ROM, QOL, and adverse/negative effects from exercise</p>

### *Risk of Bias*

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Sequence generation (selection bias)	Low Risk	The randomization was done by use of envelopes with allocation, selected by children that had already been stratified by their Children's Cancer Group (CCG) risk group, and whether they were in the 1st or 2nd half of maintenance therapy
Allocation concealment (selection bias)	Unclear Risk	Probably (for participants), since baseline measurements taken, and then randomization/ allocation occurs; but it is unclear if this would have concealed the allocation from investigators
Blinding of outcome assessors (performance bias) – CPF	Low Risk	Blinding of outcome assessment ensured (i.e., “One of two experienced physical therapists unaware of the children’s group assignment performed the pre-test assessment and post-test assessment 4 months later”); and even if the blinding could have been broken, the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding.
Incomplete Outcome Data (attrition bias) – CPF	Unclear Risk	Unclear if all participants accounted for in data tables, since there are no N values in the data table for comparison with the allocation N values for the control and intervention group, and the remark that "All but two children cooperated and participated in the testing measurements without difficulty", and "one was unable to complete the study as she needed crutches" without specificity as to which group this participant comes from.
Selective Reporting (reporting bias)	Unclear Risk	Insufficient information to permit judgement of Low risk or High risk.
Other forms of bias	Unclear Risk	Representativeness may be compromised, although this is unclear (i.e., insufficient evidence).

## Appendix XIX: Characteristics of Moyer-Mileur 2009

Methods	Design: RCT Setting: USA Randomisation: not specified Stratification: none Study Duration: not reported Treatment Status: 100% on-treatment Measurement Time Points: baseline, mid-intervention, and post-intervention
Participants	n= 13 Diagnosis: 100% standard-risk ALL Age at start of study: mean age (SD) of intervention group was 7.2 (0.7), and mean age (SD) of control group was 5.9 (0.7) Gender ratio (male:female): 3:3 in intervention group, and 4:3 in control group
Intervention	Intensity: moderate-vigorous activity; Frequency: initially a minimum 3/week; Time per session: initially a minimum of 15-20 minutes; Duration: 12-months; Aerobic exercise type: activity examples on pyramid
Outcomes	<b>CPF:</b> Progressive Aerobic Cardiovascular Endurance Run (PACER), outcome is number of 20-metre sections completed <b>Secondary Outcomes:</b> Body composition, muscle strength, flexibility

<b><i>Risk of Bias</i></b>		
<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Sequence generation (selection bias)	Unclear Risk	Unclear what exact randomization procedure was, and also unclear if any stratification occurred. All that is stated is "Subjects were randomized to a 12-month home-based exercise and nutrition program (EX) or control (CTL) group at the beginning of maintenance phase of therapy."
Allocation concealment (selection bias)	Unclear Risk	Most likely, but not stated explicitly

***Risk of Bias***

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Blinding of outcome assessors (performance bias) – CPF	Unclear Risk	Not reported whether outcome assessors were blinded to group assignment
Incomplete Outcome Data (attrition bias) – CPF	Unclear Risk	Unclear, since number enrolled/allocated vs. number evaluated with reported data was addressed - but there was “1 patient removed from the study due to lack of interest” and it is not clear if this person was an intervention or control participant, and therefore unclear which group size is altered because of this participant being removed
Selective Reporting (reporting bias)	Low Risk	The study authors decided to only report data on activity levels at baseline, 3 month, 6 month and 12 month, even though they were recorded every month. However, since they did report on some activity levels, this is not a source of high risk of bias.
Other forms of bias	Unclear Risk	A few things may compromise representativeness, although this is unclear for all of them (i.e., insufficient evidence); unclear if the restriction of the exercise test in the study is valid (i.e., "maximum of 10 minutes" for the PACER, which does not appear in the FitnessGram test administration manual).

## Appendix XX: Characteristics of Tanir 2012

Methods	Design: RCT Setting: Turkey Randomisation: not specified Stratification: none Study Duration: 10 months Treatment Status: 100% off-treatment (in remission) Measurement Time Points: baseline and post-intervention
Participants	n= 40 Diagnosis: 100% ALL Age at start of study: mean age (SD) of intervention group was 10.21 (1.51), and mean age (SD) of control group was 10.72 (1.51) Gender ratio (male:female): 15:4 in intervention group, and 9:12 in control group
Intervention	Intensity: moderate-vigorous intensity (according to Compendium of PA 2011); Frequency: 3/week; Time per session: 30 minutes; Duration: 3-months; Aerobic exercise type: step-dancing to music, jumping rope, riding a bicycle, running at a slow pace, in rhythm, walking quickly
Outcomes	<b>CPF:</b> 9-minute-run-walk test, outcome is number of 30-metre/100-foot cycles <b>Secondary Outcomes:</b> QOL, blood parameters

<b><i>Risk of Bias</i></b>		
<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Sequence generation (selection bias)	Unclear Risk	Unclear what exact randomization procedure was, and also unclear if any stratification occurred. All that is stated is "randomized selection"
Allocation concealment (selection bias)	Unclear Risk	Unclear, because there is very little detail as to the randomization procedure
Blinding of outcome assessors (performance bias) – CPF	Unclear Risk	Not reported whether outcome assessors were blinded to group assignment

### ***Risk of Bias***

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Incomplete Outcome Data (attrition bias) – CPF	Low Risk	All outcome data reported, and patients are adequately accounted for, since the 1 intervention participant who was randomized, but then met his/her demise, was accounted for
Selective Reporting (reporting bias)	Unclear Risk	Insufficient information to permit judgement of Low risk or High risk.
Other forms of bias	High Risk	There is at least one important risk of bias. One thing may compromise representativeness, specifically that none of the participants have cardiac, pulmonary, renal or hepatic dysfunction; also there is a significant baseline imbalance in gender (statistical difference between intervention and control group i.e., $p=0.014$ )

## Appendix XXI: Characteristics of Chiang 2007

Methods	Design: CCT Setting: Taiwan Randomisation: not performed Stratification: intervention group and control group matched by age and sex Study Duration: 13 months Treatment Status: 100% on-treatment Measurement Time Points: baseline and post-intervention	
Participants	n= 44 Diagnosis: 100% ALL Age at start of study: mean age (SD) of intervention group was 11.01 (3.56), and mean age (SD) of control group was 12.48 (3.86) Gender ratio (male:female)*: 6:6 in intervention group, and 6:4 in control group	
Intervention	Strategies: exercise video was given to each participant in the intervention group, developed by an exercise specialist; Intensity: moderate (according to <b>Norton et al., 2009</b> ; and <b>POEM, 2015</b> ) (i.e., the 20-minute exercise section aimed to increase the patient's HR by 40-60% HRR (i.e., 55<70% HR max)); Frequency: 3/week; Time per session: minimum 10 minutes (first 2 weeks only), maximum 30 minutes (including a 5-min warm-up aimed to increase the participant's HR by 10-30% HRR, and a 5-minute cool-down aimed to return participant's HR to warm-up level); Duration: 6 weeks; Aerobic exercise type: leisure activities and sports in a recreational environment	
Outcomes	<b>CPF:</b> Bruce treadmill protocol, outcome is relative VO2 peak <b>Secondary Outcomes:</b> Fatigue	
<b><i>Risk of Bias</i></b>		
<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Sequence generation (selection bias)	High Risk	No randomization (but participants only knew what group they were in right after they are enrolled in the study)



### *Risk of Bias*

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Allocation concealment (selection bias)	High Risk	No, since it does not sound like baseline measurements were taken before participants were enrolled in study (at which point the participants “knew what group they were in”)
Blinding of outcome assessors (performance bias) – CPF	Unclear Risk	Not reported whether outcome assessors were blinded to group assignment
Incomplete Outcome Data (attrition bias) – CPF	Low Risk	All outcome data reported; <b>N.B.</b> may be more prudent to use per-protocol analysis results since intention-to-treat analysis was potentially done with substantial departure of the intervention received from that assigned at randomization
Selective Reporting (reporting bias)	Unclear Risk	None of the study’s pre-specified outcome measures (i.e., those mentioned in the protocol) have been reported in an accessible format (i.e., both in terms of being available online and being written in English). Also, all of the outcome data that was retrieved for this study was received in an e-mail from the primary author. All of this being said, this is not a source of selective outcome reporting, because we cannot be sure whether the author(s) would have published data for all outcomes, had the study been published in an accessible format, as well as in English.
Other forms of bias	Unclear Risk	The representativeness of the sample may be compromised, but this is unclear. Also, the exercise test used has not been validated in this age group, and there are some differences in how the test was used in the study, and how it was originally designed/validated (i.e., duration of stage 0, and increases in speed in subsequent stages after stage 1)

\*Gender ratios are based on the reported data in the paper by Yeh et al<sup>222</sup> (which included fewer participants), since gender ratio information could not be determined/retrieved for Chiang.<sup>218</sup>

## Appendix XXII: Characteristics of Niesen-Vertommen 1998

Methods	<p>Design: CCT          Setting: Canada          Randomisation: not performed          Stratification:(cancer group and healthy group) matched by baseline PA level and (inadvertently) by socioeconomic status and psychological background; no matching for cancer (exercise) and cancer (control) group          Study Duration: not reported          Treatment Status: 100% off-treatment          Measurement Time Points: baseline, mid-intervention, and post-intervention</p>
Participants	<p>n= 18          Diagnosis: 44.4% ALL; 27.8% Wilm’s tumour; 11.1% rhabdomyosarcoma; 5.6% AML; 5.6% Hodgkin’s lymphoma; 5.6% neuroblastoma          Age at start of study: mean age (SD) of intervention group was 11.8 (0.6), and mean age (SD) of control group was 10.6 (0.3)          Gender ratio (male:female)*: 5:5 in intervention group, and 2:6 in control group</p>
Intervention	<p>Intensity: HR range of 50-80% of maximal HR (MHR), with an optimal training intensity window of 60-80% MHR (i.e., moderate intensity according to Norton et al., 2009; 55&lt;70% HR max); Frequency: 3/week; Time per session: beginning at 25-30 minutes, and a gradual increase each week to a maximum of 45-50 mins/session (plus a 10-min warm-up and cool-down period); Duration: 12 weeks; Aerobic exercise type: aerobic team sports such as soccer, ultimate Frisbee, dodge ball, hand ball, indoor floor hockey, and basketball; anaerobic activities included interval running, obstacle courses, and circuit training with weights and sprint activities interspersed</p>
Outcomes	<p><b>CPF:</b> Maximal graded exercise protocol (on cycle ergometer), outcomes are absolute and relative VO<sub>2</sub> peak  <b>Secondary Outcomes:</b> Sum of skin folds; spirometry measures (to assess pulmonary function); measures of anaerobic capacity; ventilation; heart rate; total time on exercise test; workload completed; results of analysis of 6 psychological domains; and echocardiography Doppler results</p>

<b><i>Risk of Bias</i></b>		
<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Sequence generation (selection bias)	High Risk	No randomization (participants were able to self-select based on their availability to enter into the exercise rehabilitation program)
Allocation concealment (selection bias)	High Risk	No, because there was no randomization (same rationale as for Dubnov-Raz 2015)
Blinding of outcome assessors (performance bias) – CPF	Unclear Risk	Not explicitly stated (potentially not blinded based on statement regarding blinding to intervention administration: "investigators were not blinded to the exercise or control group each subject participated in")
Incomplete Outcome Data (attrition bias) – CPF	Low Risk	All outcome data more or less reported (except for the two participants from one of the groups [unclear which group] that had to leave the study [unclear when they had to leave the study]); this reason for missing outcome data is unlikely to introduce significant bias/be related to true outcome.
Selective Reporting (reporting bias)	Low Risk	All pre-specified outcome measures were either reported in full, or the extent to which data was able to be collected for them was reported.

***Risk of Bias***

<b>Bias</b>	<b>Author's judgement</b>	<b>Description</b>
Other forms of bias	High Risk	<p>May not be a representative sample due to some of the inclusion/exclusion criteria (although it is <b>unclear</b> for all if this actually caused loss of representativeness); also, the fact that many participants are from the same socioeconomic group may reduce representativeness (although this is also <b>unclear</b>); the protocol used to measure VO2 peak may not be validated (let alone, in an age-matched group) (<b>unclear</b> if it is validated); the relatively lower reliability and reproducibility of cycle ergometer exercise test results (which were used in this study) than treadmill exercise test results may increase inaccuracy; the calculated sample size (for a powered result) was not met; also, the difference in age between the groups may be the cause for an overestimated difference between cancer survivors and healthy individuals due to the fact that it was found to be more "difficult to motivate the children, especially those under 10 years old, to maintain the desired heart rate intensity", AND there were seemingly more younger participants (i.e., under 10 years old) in the cancer groups</p>