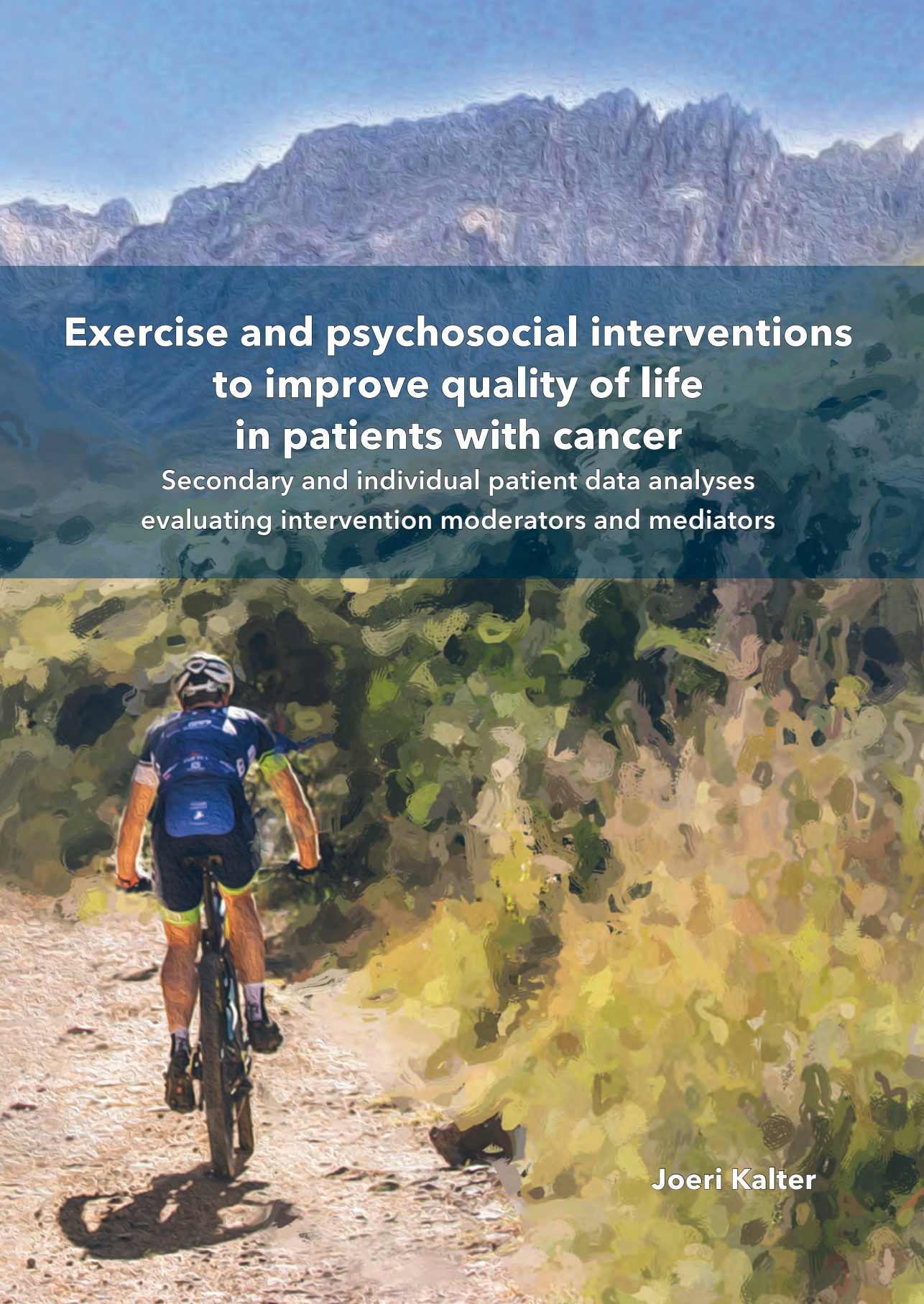

Exercise and psychosocial interventions to improve quality of life in patients with cancer

Secondary and individual patient data analyses evaluating intervention moderators and mediators

Joeri Kalter

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This thesis was prepared within the Amsterdam Public Health research institute, at the department of Epidemology and Biostatistics of the VU University Medical Center, Amsterdam, the Netherlands.

The Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study was supported by Alpe d'HuZes/Dutch Cancer Society (Grant number: VU 2011-5045).

Cover design: Iliana Boshoven-Gkini, www.AgileColor.com
Printing: GVO drukkers & vormgevers B.V., Ede

ISBN: 978-94-6332-383-3

VRIJE UNIVERSITEIT

Exercise and psychosocial interventions to improve quality of life in patients with cancer:
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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op vrijdag 28 september 2018 om 11.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door
Johannes Kalter
geboren te Losser

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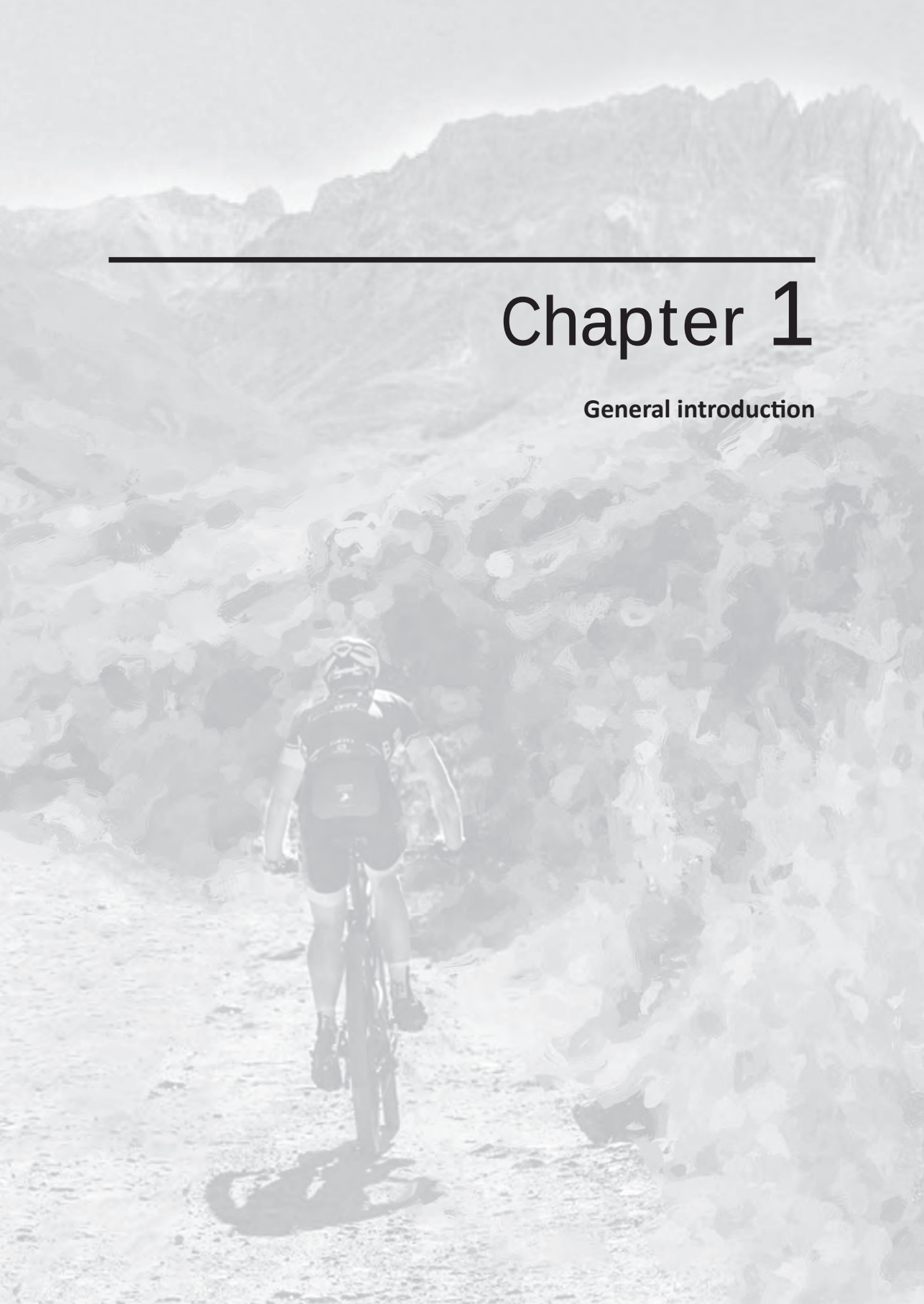
	prof.dr. I.M. Verdonck-de Leeuw
copromotor:	dr. L.M. Buffart

Table of contents



Chapter 1

General introduction

Cancer, treatment, and treatment-related symptoms

Cancer counts for 14 million new cases worldwide every year, and the number of new cases is expected to rise by 70% over the next two decades due to aging and growth of the population [1]. Lung, prostate and colorectal cancer are the most commonly diagnosed types of cancer among men worldwide, accounting for 17%, 15% and 10% of the total cancer diagnosis, respectively. Breast (25%), colorectal (9%) and lung cancer (9%) are the most commonly diagnosed cancers among women worldwide [1]. In the Netherlands, the number of people diagnosed with cancer increased from 64,604 in 1995 to 105,844 in 2015 [2], and it is expected that the number of patients with cancer will increase up to 666,000 in 2020 [3]. The most prevalent cancer types in the Netherlands are breast, skin, and prostate cancer, representing 56% of all new cases [2].

In the last decades, cancer survival rates have increased substantially, but differs greatly between cancer types. In the Netherlands, the overall 5-year cancer survival rate has increased from 47% in 1989-1993 to 64% in 2011-2015 [2]. These improvements in survival rates are caused by advances in early cancer detection (i.e. diagnosis and screening) and more effective treatments [4]. Advances in radiation, chemotherapy, immunotherapy, and targeted treatments have improved survival, especially for cancer of the breast, prostate, lung, liver, melanoma, and colon or rectum [5, 6]. The type of treatment(s) used depends on the location and size of the tumor, the presence of metastases, and the general health status of the patient [1].

Unfortunately, many patients with cancer are confronted with physical and psychosocial problems that may persist years after treatment [7, 8]. For example, cancer-related fatigue is reported in up to 90% of the patients during treatment [9, 10], and in one-quarter of patients with breast cancer, it may persists for up to 5 years after completion of treatment [10]. It has also been shown that cardiorespiratory fitness of patients with breast cancer is 31% lower during adjuvant therapy and 22% lower after adjuvant therapy compared to age-matched healthy sedentary women [11]. In addition, androgen deprivation therapy, commonly used in the treatment of patients with prostate cancer, may decrease muscle mass by 2% to 4% within 3 to 12 months of initiation of treatment [12-14]. Also, muscle mass decreased during chemotherapy by 6.1% in patients with metastatic colorectal cancer [15]. Loss of muscle mass is associated with reduced muscle strength [16], poorer physical

function [17] and fitness [18], and poorer survival [15]. Furthermore, depression and anxiety disorder, as measured by a diagnostic interview is prevalent in 14% and 10% of patients with cancer during treatment, respectively [19, 20]. Prevalence of symptoms of depression and anxiety (based on patient reported outcome measures) is estimated to be much higher (27% [20] and 26% [21], respectively). In patients with cancer who were at least 2 years after diagnosis, the prevalence of depression and anxiety disorder is estimated to be 8% and 18%, respectively [22]. These physical and psychosocial problems are associated with reduced health-related quality of life (QoL) [23, 24]. QoL is a subjective multidimensional health outcome, encompassing physical, emotional and social functioning, symptom burden and perceived health status [25, 26]. With the increasing number of patients with cancer in the coming decades, the demand for developing intervention strategies that not only focus on treating the cancer itself, but also on preventing or reducing physical problems, and maintaining or improving QoL will rise as well [27-33].

Exercise and psychosocial interventions

Previous studies showed that physical activity (i.e. any bodily movement that results in energy expenditure [34]), exercise (i.e. a form of physical activity that is planned, structured and repetitive and aims to improve fitness, performance or health [34]) and/or psychosocial interventions improve physical and/or psychosocial function and QoL in patients with cancer [27-33]. It is hypothesized that physical inactivity induces muscle catabolism and causes further detraining, which may result in a self-perpetuating detraining state with easily induced cancer-related fatigue [24, 35]. Physical activity and exercise may interfer this self-perpetuating cycle by improved physical fitness, and consequently reduced cancer-related fatigue and improved QoL [24, 35]. Furthermore, psychosocial interventions may help to reduce psychological distress, depression, anxiety, and fatigue, and to reduce sleep problems, and subsequently improve the patient's QoL [30-33].

Exercise interventions may have different dimensions with respect to the mode of intervention delivery (e.g. supervised or unsupervised), intervention duration and timing, or exercise frequency (e.g. number of exercise sessions per week), intensity (e.g. low, moderate, or high intensity), type (e.g. aerobic, resistance, or impact training) and time (i.e. session duration) [36]. Psychosocial interventions

for patients with cancer can be categorized into different types. Cunningham's hierarchic classification distinguishes five types of heterogenetic psychosocial interventions based on the degree of psychological change the different interventions seek to promote in patients with cancer: (I) information provision, i.e. interventions aimed at increasing the patient's knowledge of cancer, its treatments, side effects and consequences; (II) support, i.e. interventions intended to help patients to cope with the implications of cancer and its treatment, e.g. express associated emotions, diminish a sense of isolation, identify unmet needs, take some control over events, deal with family members and health care personnel and accept losses and changed roles; (III) coping skills training, i.e. interventions targeted at attaining new cognitive-behavioral skills such as relaxation, mental imaging, thought and affect management and activity planning; (IV) psychotherapy, i.e. interventions delivered by a well-trained professional that aim to achieve a more fundamental psychological change to increase self-understanding via, for example, psychodynamic therapy and supportive-therapeutic approaches; and (V) spiritual or existential therapy, i.e. interventions promoting experiential awareness of a transcendent order or power, some sense of belonging to a meaningful universe including mediation and prayer (where meaningful to the patient), appropriate reading, discussion and reflection around spiritual topics [37]. In addition, psychosocial interventions may exist in different durations, formats (e.g. individual, group, or couple therapy), methods (e.g. face-to-face, telephone, or web-based), and can be delivered by different professions (e.g. psychologist or nurse) and at different moments (e.g. during or after primary cancer treatment).

Optimizing QoL with exercise and psychosocial interventions

Previous meta-analyses have evaluated the effectiveness of exercise and psychosocial interventions on QoL in patients with cancer [27-33]. In most studies, significant and positive effects on QoL were observed, although the mean effect sizes were small-to-moderate [27-33]. One possible explanation for the small effect sizes of exercise and psychosocial interventions is that these interventions are often evaluated in a heterogeneous group of patients with cancer and are not sufficiently targeted to specific cancer populations with the highest needs [38], or tailored to specific characteristics of patient groups. The development of targeted interventions can

contribute to more effective intervention programs [39]. It is therefore important to identify subgroups of patients that respond best to the intervention, by conducting moderation analysis [38]. Moderators are variables that affect the direction and/or strength of the relation between the intervention and outcome [40, 41]. This will inform clinical practice such that some interventions may only be used for a particular subgroup of patients with cancer, ensuring optimal use of limited resources [42].

Few previous studies have found that demographic, clinical and personal factors may moderate the effects of exercise and psychosocial interventions on QoL [43-47]. However, as these single studies have insufficient power to conduct stratified analyses by the moderator subgroup, the moderator effects found in previous single studies should be interpreted as exploratory analyses [38]. Thus, to study the moderators of exercise and psychosocial interventions on QoL, and to conduct subsequently stratified analyses by the moderator subgroup, a study with a much larger sample size is needed [38].

To further improve the effectiveness of exercise and psychosocial interventions on QoL among patients with cancer, insights in the working mechanisms of an intervention (i.e. insight into the mediators of the effect of an intervention) are needed [38, 48, 49]. Intervention mediators are intermediate variables that explain how or why an intervention influences an outcome [38].

Identification of mediators may help identify effective intervention components. By keeping effective intervention components and by removing ineffective ones, the cost-effectiveness and participant burden of the interventions can be improved [50]. Furthermore, identification of mediators may support in the building and refining of intervention theory [51]. For example, previous studies have shown that fatigue and psychological distress may mediate the relationship between physical activity and QoL [52, 53]. In addition, exercise effect on QoL may be mediated by physical activity, self-efficacy, mastery, fatigue, and distress [54]. However, studies investigating mediators of exercise and psychosocial intervention effects on QoL are scarce.

Predicting OptimaL Cancer RehabIlitation and Supportive care (POLARIS) study

Meta-analyses that synthesize results of different individual studies inform health professionals about the best available treatment and are an integral part of evidence based medicine [55, 56]. An important aspect of a meta-analysis is the ability to explore whether intervention effects vary or are moderated by study characteristics (e.g. type or duration of intervention) [57]. Subgroup analyses or meta-regression, in which the change in overall intervention effect in relation to study-level characteristics is investigated, are used to compare intervention effects across different modes of intervention or across different patient populations [57]. Summary data can be used to investigate these sorts of study-level interactions. However, to investigate interactions between the intervention and patient-level characteristics (e.g. age or stage of cancer), a meta-regression relies on summary data, such as the mean age of the patients [56, 57]. In contrast, a meta-analysis that uses individual patient data (IPD) is not limited to using summary data. It obtains and harmonize the raw IPD from multiple related studies [56], and has the advantage to test interactions between interventions and patient-level characteristics using the large number of raw data points, conducting subsequent stratified analyses, and standardized analytic techniques across the included studies [58, 59]. IPD meta-analysis is therefore considered the 'gold-standard' to evaluate moderators of intervention effects with sufficient power [56, 60, 61], and it will help to ensure that clinical practice and research is informed by robust evidence about the effect of interventions [57].

To study moderator effects of exercise and psychosocial interventions on QoL, the Predicting OptimaL Cancer RehabIlitation and Supportive care (POLARIS) study has been set up. For POLARIS, an international consortium and a database of IPD from multiple randomized controlled trials was created to (I) conduct an IPD meta-analysis to evaluate the effects of exercise and psychosocial interventions on the QoL in patients with cancer compared to a wait-list, usual care or attention control group, and to (II) identify demographic, clinical and personal characteristics, and intervention-related characteristics that moderate the effects of exercise and psychosocial interventions on QoL.

One of main challenges of an IPD meta-analysis is to harmonize raw data of

single studies. Harmonizing IPD from single studies is a timely endeavor, particularly when many eligible studies are available [62]. Difficulties may arise with harmonizing IPD as different studies often use different coding schemes or constructs [63]. A platform that enables harmonizing as soon as IPD from the first studies has been received is more time-efficient, especially when the number of variables and datasets are large. Thus, a flexible data harmonization platform that enables harmonizing data during data collection is therefore useful. To our knowledge, a platform allowing this flexible approach has not yet been developed.

Aims and outline of this thesis

This thesis aims to (I) investigate the effects of exercise and psychosocial interventions on QoL in patients with cancer during and after treatment and to assess the possible moderators of these intervention effects; (II) investigate the mechanisms of exercise interventions on QoL; and (III) build a flexible data harmonization platform that facilitates harmonizing data starting already during data collection.

Chapter 2 explores demographic, clinical and psychological moderators of the effect of a group-based physical exercise intervention on global QoL in patients with cancer who completed treatment. In this chapter, the moderator effects of age, gender, education level, marital status, employment status, type of treatment, time since treatment, the presence of comorbidities, fatigue, general self-efficacy, depression and anxiety are studied. Chapter 3 explores physical and psychological mediators of a combined resistance and endurance exercise intervention effect on QoL and physical function. This chapter investigates the hypothesis that combined resistance and endurance exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and improving global QoL and physical function among patients with cancer who completed curative treatment including chemotherapy. Chapter 4 describes the design of the POLARIS study which was set up to evaluate the effects of exercise and psychosocial interventions on the QoL of patients with cancer, and to identify demographic, clinical, and intervention-related moderators of these intervention effects. Chapter 5 contains the description of the development and use of a flexible data harmonization platform that facilitates harmonization of IPD for meta-analyses as used in the POLARIS study. Chapter 6 and 7 present the results of the POLARIS study, evaluating the effects of exercise

and psychosocial interventions, respectively, on QoL in patients with cancer, and studying demographic, clinical and intervention-related moderators of intervention effects. Finally, Chapter 8 summarizes and discusses the main findings of this thesis, methodological issues, clinical implications, and provides suggestions for future research.

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Chapter 2

Moderators of the effects of group-based physical exercise on cancer survivors' quality of life

Joeri Kalter, Laurien Buffart, Irene Korstjens, Ellen van Weert, Johannes Brug, Irma Verdonck-de Leeuw, Ilse Mesters, Bart van den Borne, Josette Hoekstra-Weebers, Wynand Ros, Anne May

Supportive Care in Cancer 2015; 23: 2623–2631

Abstract

Purpose: This study explored demographic, clinical, and psychological moderators of the effect of a group-based physical exercise intervention on global quality of life (QoL) among cancer survivors who completed treatment.

Methods: Cancer survivors were assigned to a 12-week physical exercise (n=147) or a wait-list control group (n=62). The main outcome measure was global QoL, assessed with the EORTC QLQ-C30 at baseline and 12 weeks later. Potential moderators were age, gender, education level, marital status, employment status, type of treatment, time since treatment, the presence of comorbidities, fatigue, general self-efficacy, depression and anxiety. Linear regression analyses were used to test effect modification of the intervention by each moderator variable using interaction tests ($p \leq 0.10$).

Results: The physical exercise intervention effect on global QoL was larger for cancer survivors who received radiotherapy (β= 10.3, 95% CI= 4.4; 16.2) than for cancer survivors who did not receive radiotherapy (β= 1.8, 95% CI= -5.9; 9.5, $p_{interaction}$=0.10), larger for cancer survivors who received a combination of chemo-radiotherapy (β= 13.0, 95% CI= 6.0; 20.1) than for those who did not receive this combination of treatments (β= 2.5, 95% CI= -3.7; 8.7, $p_{interaction}$=0.02), and larger for cancer survivors with higher baseline levels of fatigue (β= 12.6, 95% CI= 5.7; 19.6) than for those with lower levels (β= 2.4, 95% CI= -3.9; 8.7, $p_{interaction}$=0.03). No other moderator effects were found.

Conclusions: This study suggests that cancer treatment modality and baseline fatigue levels moderate the effect of a physical exercise program on cancer survivors' global QoL.

Introduction

Due to advances in detection and treatment of cancer, the number of cancer survivors in Western countries has increased substantially over the last decades, and is expected to rise in the years to come [1]. In Europe, the 5-year cancer survival rate has increased from 8 million in 2002 to 9.8 million in 2012 [2, 3]. Despite increased survival rates, however, many cancer survivors experience physical and psychological problems related to the disease and its treatment, such as increased fatigue, anxiety, depression and decreased physical fitness and function [4]. These problems negatively affect the cancer survivors' QoL [5].

Several meta-analyses have shown that physical exercise can improve their QoL, but reported effect sizes were small to moderate (range 0.29-0.48) [6-9]. In a physical exercise study performed in the Netherlands, we found a moderate effect (Cohen's d=0.51) of a 12-week group-based physical exercise program on global QoL of cancer survivors who completed cancer treatment compared to a wait-list comparison group (WLC). In addition, 53% of cancer survivors who completed the program had a clinically relevant improvement (>10 points) in global QoL [10].

One possible explanation for the small to moderate effect sizes is that these interventions were offered to a heterogeneous group of cancer survivors and were not sufficiently targeted to the specific populations with highest needs [11]. It is therefore important to investigate which subgroups of survivors are most likely to benefit from a physical exercise program. Insight into these moderators will help to determine which specific survivors should be referred to a particular exercise intervention [12].

In previous studies among survivors undergoing treatment for breast cancer [13], and lymphoma [14], Courneya and colleagues showed that demographic and clinical variables, baseline health, and psychological function may moderate the physical exercise effects on QoL. Aerobic exercise had larger effects on QoL in survivors with breast cancer who were not married compared to those who were [13]. Compared to their counterparts, resistance exercise effects were larger for breast cancer survivors who were not married, and had a preference for resistance exercises [13]. In cancer survivors with lymphoma, greater benefits of aerobic exercise on QoL were found in cancer survivors who were unmarried, had normal weight or were obese, or were in poor/fair health compared to cancer survivors

who were married, overweight (but not obese), and in good health, respectively [14].

The current analyses used data from our previous trial that evaluated the effects of a 12-week group-based physical exercise program among cancer survivors who completed cancer treatment [10, 15, 16]. The aim of the present analyses was to explore which demographic (age, gender, education level, marital status, and employment status), clinical (type of treatment, time since treatment, presence of comorbidity), and psychological (fatigue, self-efficacy, symptoms of depression and anxiety) characteristics moderated the physical exercise effects on cancer survivors' global QoL.

Materials and methods

Recruitment and allocation

This study is part of a multicenter randomized controlled trial evaluating the effects of group-based physical exercise on cancer survivors' QoL [10, 15, 16]. Detailed descriptions of the study procedures are published elsewhere [10, 15, 16]. The trial was conducted at four rehabilitation or medical centers in the Netherlands [10, 15, 16]. The medical ethics committees of the University Medical Center Utrecht and the local centers approved the study.

Participants aged ≥18 years, who had completed cancer treatment at least 3 months before study entry, and had an estimated life expectancy ≥1 year were recruited between February 2004 and December 2005. After a written consent, these cancer survivors completed baseline measurements and were randomized to physical training (PT) or PT plus cognitive behavioral therapy (PT+CBT). In each center consecutive groups of 8 to 12 eligible subjects were assigned to the randomly determined treatment to ascertain adequate numbers of participants in each group. An independent researcher randomly determined the sequence of interventions at each center, using a randomization list. The number of PT and PT+CBT groups were balanced in each center. In addition, eligible cancer survivors were invited to participate in a WLC group if, because of full rehabilitation groups, they had to wait at least 3 months to start with a 12-week group-based multidisciplinary cancer rehabilitation program in other Dutch centers than the four recruiting centers.

In total, 209 cancer survivors participated in the study; 71 were allocated to PT, 76 to PT+CBT, and 62 to WLC. Measurements were performed at baseline and after 12 weeks. Participants' adherence rates were 84% of the total number of 24 PT sessions and 82% of 12 CBT sessions. In total, 196 cancer survivors (94%) completed the post-intervention assessment [15]. No differences in changes from pre-intervention to post-intervention in physical fitness, fatigue, distress, and QoL were found between PT and PT+CBT groups [10, 15, 16]. In the present study, we therefore combined the two intervention groups into one group. However, differences between moderating effect between the intervention groups may be present. We therefore added a sensitivity analyses to check whether a difference of moderating effect between the intervention groups existed.

Interventions

Detailed descriptions of PT and CBT are provided elsewhere [16, 17]. PT was supervised by two physical therapists and CBT by a psychologist and a social worker, all experienced professionals in cancer rehabilitation. PT took place twice per week, for 12 weeks, in groups of 8-12 cancer survivors and included individual aerobic training (20-30 minutes), muscle strength training (20-30 minutes), and group sports (60 minutes). Intensity of the individual aerobic training was based on the maximum heart rate determined during baseline symptom-limited ergometry and the Karvonen formula. Exercise training was performed at a heart rate of [heart rate at rest + 40-50% of (peak heart rate-heart rate at rest)] during the first 4 weeks and gradually increased to a heart rate of [heart rate at rest + 70-80% of (peak heart rate-heart rate at rest)] in week 12.

Intensity of the muscle strength training was based on baseline individual 1-repetition maximum (1-RM). Training intensity started at 30% of the 1-RM during the first week and increased to 50-60% of 1-RM in week 12. Group sports was included to promote enjoyment and adoption of a physically active lifestyle. Cancer survivors also received information about the benefits of exercise and, depending on their individual goals, also on coping with fatigue, restoration of the balance between demand and capacity during tasks and activities, exercise physiology, illness perceptions and self-management to support them in regulating their physical activity.

The interventions were based on the principles of group-based self-management: i.e. goal selection, information collection, information processing and evaluation, decision making, action and self-reaction [18]. These principles were incorporated by setting and monitoring personal training goals, and monitoring training progress using exercise logs, heart rate monitors, and the Borg Scale for dyspnea and fatigue. Self-efficacy improvement strategies included encouraging mastery experiences by starting at low intensity, improvements in physiological arousal by improving exercise capacity, verbal persuasion to perform training activities, and enhancing vicarious learning through the group format delivery [19].

CBT was conducted once a week for 12 weeks, in 2 hour group sessions and aimed to train self-management skills using a cognitive-behavioral problems solving approach [20]. This approach aimed at finding effective and adaptive solutions to stressful problems and at changing dysfunctional cognition, emotions, and behaviors [21]. It included discussions on distress, exercise physiology, relaxation (sessions 1 to 4), and training self-management skills to realize personal goals (sessions 5 to 12). During this process, also problem orientation, problem definition and formulation and goal setting, generation of alternative solutions (brainstorming), decision making, and solution implementation and verification were discussed.

Measures and measurements

Outcome

Global QoL was assessed at baseline and 12 weeks later using the subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [22]. The EORTC QLQ-C30 is a reliable and valid instrument that has been used in many studies evaluating clinical and psychosocial interventions with cancer survivors [22]. The subscale used includes two questions addressing perceptions of general health and overall QoL. After applying a linear transformation procedure according to the manual, the scores of the scale range from 0 to 100, with higher scores representing a higher global QoL.

Potential moderators

Demographic and clinical characteristics

Demographic characteristics including age, gender, education level, marital status, and employment status were collected at baseline using a self-reported questionnaire. We dichotomized education level into low (elementary and lower vocational education) versus high (secondary and secondary vocational education, higher vocational and university education), marital status into single versus married and/or living together, and employment into employed versus unemployed at diagnosis.

Clinical characteristics were collected using a self-report questionnaire including type of cancer, type of treatment received, time since completion of treatment, cancer recurrence, and presence of comorbidity. We dichotomized the treatment regimens surgery, radiotherapy, chemotherapy, and a combination chemo-radiotherapy into received versus not received. Cancer survivors who were categorized in the combination chemo-radiotherapy group were also categorized in the radiotherapy, and the chemotherapy group. Disease recurrence was dichotomized into no or unknown versus yes and presence of comorbidity into none versus any. Cancer survivors with comorbidity reported to receive medical treatment for one or more of the following problems: cardiac problems, vascular problems, diabetes, asthma, rheumatic problems, musculoskeletal problems, psychological problems or other complaints. Clinical characteristics were confirmed by the referring physicians.

Psychological characteristics

General fatigue

General fatigue was assessed at baseline with the 4-item general fatigue subscale of the Multidimensional Fatigue Inventory (MFI) [23]. The total MFI consists of 20 statements for which a person indicates the extent to which, during the previous few days, a particular statement applies to him or her on a 5-point scale. The possible range for the general fatigue subscale is 4-20, with higher scores indicating higher levels of fatigue. The Multidimensional Fatigue Inventory has good internal

consistency (average Cronbach's alpha=0.84) [23].

General self-efficacy

General self-efficacy was measured at baseline with the standardized Dutch version of the General self-efficacy scale [24]. This 16-item questionnaire yields a total-score and three subscales: willingness to expend effort in completing a behavior, persistence in the face of adversity, and willingness to initiate behavior. The total score, with a possible range from 16-80, was used for further analysis with higher scores representing higher self-efficacy.

Anxiety and depression

Anxiety and depression were assessed at baseline with the 14-item Hospital Anxiety and Depression Scale (HADS) [25], validated for the Dutch population [26] and cancer survivors [27]. The HADS contains an anxiety and a depression subscale, both ranging from 0-21 points. A score ≥8 on the subscale was used to indicated possible anxiety or depression [28].

Statistical analysis

Baseline characteristics are presented as means and standard deviations (SD) or as numbers and percentages. Moderation analyses were conducted according to procedures proposed by Aguinis et al. [29]. First, we tested the underlying assumption of homoscedasticity among the moderator categories, indicating that the residual variances (i.e. the error variances that remain after predicting a dependent variable from the independent variables) are constant across the moderator categories. To test this assumption, we used the computer program ALTMMR. This program provides four tests: Deshon and Alexander's rule for homogeneity, Bartlett's test, James's test, and Alexander's test [30-33]. Homoscedasticity was assumed if three or more tests indicated homogeneous residual variances [29].

Second, we examined the achieved power for each moderator and the sample sizes required to be able to conduct subgroup analysis with a power of 80%.

For categorical moderators, we used the POWER computer program developed by Aguinis et al. [34]. For continuous moderators, we used the computer program GPower developed by Faul et al [35].

Third, we used linear regression analysis to test effect modification of the intervention by each moderator variable in the form of an interaction test [36]. Global QoL was modelled to compare changes over time across intervention-moderator groups. The analyses were adjusted for the baseline value of the outcome, marital status, educational level, and disease recurrence. The latter three variables were included because they differ significantly between the intervention and control group [10, 15, 16]. If homoscedasticity was not assumed, we used weighted least squares regression analyses. In this analysis, a weight factor was added in the analysis to adjust the residual error variance of the model [36]. The weighted factor was calculated for each moderator group by the number of degrees of freedom of the residual variation divided by the sum of squares of the residual variation.

We conducted stratified analysis to examine the intervention effect in the different moderator categories. In case of a continuous moderator, conditional effect of the intervention on global QoL after the exercise intervention was examined for the -1SD, mean and +1SD values. A variable was considered a potential moderator when the p-value of the interaction term was ≤0.10. In that case, we examined differences in intervention adherence across moderator subgroups with the student's t-test.

Finally, we calculated Cohen's f^2 effect sizes [37] providing an estimate of the variance explained by the interaction term [37]. In case of continuous moderators or homoscedasticity in categorical moderators, effect sizes were calculated by $f^2 = R_2^2 - R_1^2$, where R_2^2 is the proportion of variance accounted for with all variables in the model (including the interaction term), and R_1^2 is the proportion of variance accounted for with all variables without the interaction term in the model. In case of heteroscedasticity in categorical moderators, effect sizes were calculated by $f^2 = R_2^2 - R_1^2 / 1 - R_2^2$. We used Cohen's cut off points for multiple regression modeling of f^2=0.02, f^2=0.15, and; f^2 =0.35 to indicate a small, medium or large effect, respectively [37].

We used SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) to conduct the analyses.

Results

The mean age of cancer survivors in the exercise group was 48.8 (SD=10.9) years, 84% were female and 56% were diagnosed with breast cancer (Table 2.1). Cancer survivors in the WLC group were on average 51.3 (SD=8.8) years old, 90% were female and 61% were diagnosed with breast cancer.

Homoscedasticity was found for gender, education level, marital status, employment status, presence of comorbidity, and anxiety (Table 2.2). Heteroscedasticity was found for radiotherapy, chemotherapy, combination chemo-radiotherapy, and depression. The achieved power for the categorical variables varied between 0.6% for marital status and 54% for combination chemo-radiotherapy (Table 2.2).

We found a small (f^2=0.02, $p_{interaction}$=0.10) interaction effect of radiotherapy, indicating that the exercise intervention effect on global QoL was larger for cancer survivors who received radiotherapy (β= 10.3, 95% CI= 4.4; 16.2) than for those who did not (β= 1.8, 95% CI= -5.9; 9.5). No statistical significant ($p_{interaction}$=0.14) moderation effect was found for chemotherapy. However, sensitivity analyses showed a significant ($p_{interaction}$=0.01) moderation effect between the intervention groups in favor of the PT+CBT group. Comparing cancer survivors who received a combination of chemo-radiotherapy and those who received one or none of these treatments, we found a significant interaction effect ($p_{interaction}$=0.02) in favor of cancer survivors who received a combination of chemo-radiotherapy (β= 13.1, 95% CI= 6.0; 20.1) than for those who did not (β= 2.5, 95% CI= -3.7; 8.7) (Figure 2.1). In addition, we found a small (f^2=0.02) but significant ($p_{interaction}$=0.03) interaction effect of fatigue, indicating that the exercise intervention effect on global QoL is larger for cancer survivors with higher baseline levels of fatigue (β= 12.7, 95% CI= 5.7; 19.6) than for those with lower baseline fatigue levels (β= 2.4, 95% CI= -3.9; 8.7, Figure 2.2). No differences in adherence were found for all subgroups.

Table 2.1. Distribution of potential moderators by group assignment

Variable	Physical exercise group (n=147)	Wait list comparison group (n=62)
Demographic		
Age, mean (SD) years	48.8 (10.9)	51.3 (8.8)
Gender, n (%)		
Male	24 (16)	6 (10)
Female	123 (84)	56 (90)
Education level, n (%)*		
Low	20 (14)	16 (26)
Middle	72 (49)	32 (52)
High	55 (37)	14 (22)
Marital status, n (%)*		
Single	43 (29)	7 (11)
Married	104 (71)	55 (89)
Employment status, n (%)		
Not employed at diagnosis	40 (28)	16 (26)
Employed at diagnosis	107 (73)	46 (74)
Clinical		
Type of cancer, n (%)		
Breast	82 (56)	38 (61)
Hematological	23 (16)	10 (16)
Gynecological	18 (12)	7 (11)
Urologic	9 (6)	0 (0)
Lung	4 (3)	4 (7)
Colon	3 (2)	2 (3)
Other	8 (5)	1 (2)
Radiotherapy, n (%)		
No	63 (43)	23 (37)
Yes	84 (57)	39 (63)
Chemotherapy, n (%)		
No	47 (32)	21 (34)
Yes	100 (68)	41 (66)
Radiotherapy and chemotherapy, n (%)		
No	87 (59)	35 (56)
Yes	60 (41)	27 (44)
Time since treatment, mean (SD) years	1.3 (1.7)	1.9 (2.7)
Recurrence >3 months ago*		
No	133 (90)	47 (76)
Yes	14 (10)	15 (24)

Table 2.1 (continued)

Variable	Physical exercise group (n=147)	Wait list comparison group (n=62)
Presence of comorbidity, n (%)		
No comorbidity	79 (54)	34 (55)
Comorbidity	68 (46)	27 (43)
Psychological		
General fatigue (MFI), mean (SD)	15.6 (3.4)	15.0 (3.3)
General self-efficacy (ALCOS), mean (SD)	44.0 (8.8)	42.6 (8.5)
Depression (HADS)		
No (<8)	104 (71)	35 (57)
Yes ≥8)	43 (29)	27 (43)
Anxiety (HADS)		
No (<8)	77 (52)	34 (55)
Yes (≥8)	70 (48)	28 (45)
Global QoL (EORTC QLQ-C30), mean (SD)	57.1 (17.6)	60.1 (18.4)

* Significant differences between exercise and wait list comparison groups using chi-squared tests, p<0.05. Abbreviations: ALCOS= General self-efficacy scale; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HADS= Hospital Anxiety and Depression Scale; MFI= Multidimensional Fatigue Inventory; QoL= quality of life; SD= standard deviation

Table 2.2. Exercise intervention effects on global quality of life (QoL), stratified by potential moderator subgroups

		Intervention effect on global QoL				
Moderator	**n**	**β (95% CI)** [b]	**$p_{interaction}$** [b]	**f^2**	**ESP**	**n ($P_{80\%}$)**
Demographic						
Age, years	196		0.13	0.01	0.29	787
-1SD (39.4)		11.0 (3.7; 18.3)				
Mean (49.7)		7.1 (2.3; 11.9)				
+1SD (60.0)		3.2 (-3.4; 9.8)				
Gender [a]			0.73	0.001	0.16	
Male	28	8.9 (-4.9; 22.6)				154
Female	168	6.3 (1.2; 11.4)				924
Education level [a]			0.78	0.0003	0.03	
Low	34	8.2 (-2.0; 18.5)				374
Middle or high	162	6.7 (1.3; 12.0)				1782

Table 2.2 (continued)

		Intervention effect on global QoL				
Moderator	**n**	**β (95% CI)** [b]	**$p_{interaction}$** [b]	**f^2**	**ESP**	**n ($P_{80\%}$)**
Marital status [a]			0.56	0.001	0.02	
Single	48	10.3 (-1.9; 22.5)				360
Married	148	6.4 (1.2; 11.6)				1110
Employment status [a]			0.50	0.002	0.12	
Not employed at diagnosis	52	4.50 (-4.6; 13.6)				260
Employed at diagnosis	144	8.1 (2.6; 13.6)				720
Clinical						
Radiotherapy [a]			0.10	0.02	0.23	
No	81	1.8 (-5.9; 9.5)				230
Yes	115	10.3 (4.4; 16.2)				330
Chemotherapy [a]			0.14	0.02	0.37	
No	62	2.0 (-6.2; 10.1)				155
Yes	134	9.8 (3.9; 15.7)				335
Radiotherapy and chemotherapy			0.02	0.03	0.54	180
No	87	2.5 (-3.7; 8.7)				140
Yes	122	13.1 (6.0; 20.1)				
Time since treatment in years	196		0.14	0.01	0.29	787
-1SD (0.1)		4.8 (-0.8; 10.5)				
Mean (1.5)		6.9 (2.1; 11.7)				
+1SD (3.6)		10.1 (3.8; 16.4)				
Presence of comorbidity [a]			0.88	0.0001	0.15	
No comorbidity	102	6.7 (0.2; 13.1)				273
Comorbidity	93	7.4 (0.4; 14.4)				253
Psychological						
General fatigue	196		0.03	0.02	0.50	395
-1SD (12.1)		2.4 (-3.9; 8.7)				
Mean (15.4)		7.5 (2.7; 12.3)				
+1SD (18.8)		12.7 (5.7; 19.6)				
General self-efficacy	196		0.20	0.01	0.29	787
-1SD (35.1)		9.9 (3.1; 16.6)				
Mean (43.9)		6.7 (1.9; 11.5)				
+1SD (52.6)		3.6 (-3.2; 10.4)				
Depression			0.67	0.002	0.30	
No (<8)	131	5.9 (-0.3; 12.0)				262
Yes (≥8)	65	8.0 (0.4; 15.6)				130

Table 2.2 (continued)

		Intervention effect on global QoL				
Moderator	**n**	**β (95% CI)** [b]	**$p_{interaction}$** [b]	**f^2**	**ESP**	**n ($P_{80\%}$)**
Anxiety [a]			0.64	0.001	0.22	
No (<8)	105	6.0 (-0.3; 12.3)				258
Yes (≥8)	91	8.3 (1.1; 15.5)				223

Regression coefficients (β), 95% confidence intervals (CI), and p-value of the interaction test ($p_{interaction}$) are presented as well as Cohen's effect size (f^2) and estimated statistical power (ESP) for the interaction effect, and the number of cancer survivors needed for estimated statistical power of 80% (n ($p_{80\%}$)). Abbreviations: SD= standard deviation. [a] No violation of homogeneity of error variances was assumed; [b] Adjusted for marital status, education level, disease recurrence, and global quality of life measured at baseline.

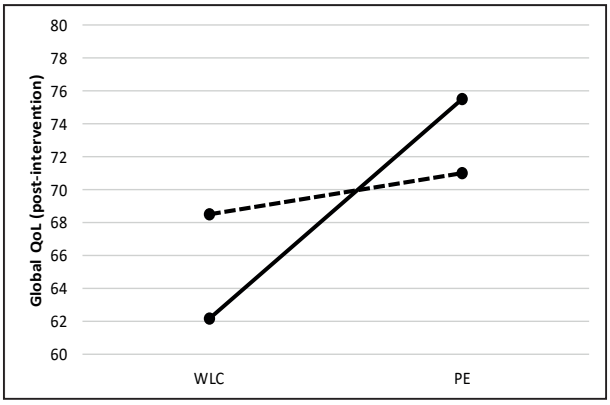

Figure 2.1. Differences in mean global quality of life (Global QoL) post intervention between waiting list control group (WLC) and physical exercise group (PE) according to having received a combination of chemo-radio-therapy (solid line) or one or none of these treatments (dotted line)

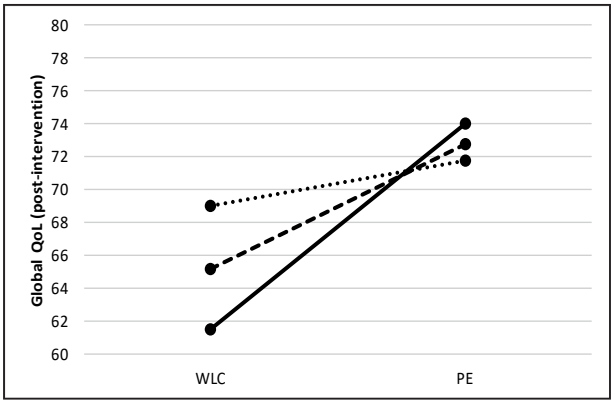

Figure 2.2. Differences in mean global quality of life (Global QoL) post intervention between waiting list control group (WLC) and physical exercise group (PE) according to low general fatigue (one standard deviation (SD) below the mean of general fatigue; dotted line), mean general (dashed line), and high general fatigue (one SD above the mean of general fatigue; solid line)

Discussion

In the current analyses, we explored moderators of physical exercise effects on global QoL. We found larger intervention effects for cancer survivors who received radiotherapy, and particularly for survivors who received the combination chemo-radiotherapy compared to those who did not. Further, we found differences in intervention effects for cancer survivors who received chemotherapy in the PT+CBT group compared to those who did not. Differences in intervention effects could not be explained by differences in adherence to the physical exercise program.

Cancer survivors who received the combination chemo-radiotherapy improved 13 points (95% CI= 6; 20) on the global QoL scale, which is larger than the clinically meaningful difference of 10 points [38]. In contrast, the intervention effect on global QoL was 2 points (95% CI= -6; 10) for cancer survivors who were treated with one of these treatments or none. The mechanism underlying the moderating effect of treatment type on QoL is unclear. Perhaps, receiving both types of treatments may have had a larger impact on the cancer survivors' QoL, and consequently leaving more room for improvement by physical exercise [39]. However, we found no statistically significant differences in baseline values of QoL between cancer survivors who received both radiotherapy and chemotherapy and those who received one or none of these treatments. Therefore, and due to the relatively small sample size and the exploratory nature of our analysis, our findings should be interpreted with caution. Future studies should examine whether cancer survivors who received different treatment regimens respond differently to physical exercise.

Baseline fatigue also moderated the exercise intervention effects on global QoL. Improvements in global QoL were 12 points higher in cancer survivors with high baseline levels of fatigue (≥1 SD above the mean) compared to those with low baseline levels of fatigue (≥1 SD below the mean), which was a clinically meaningful difference [38]. Differences in effects could not be explained by differences in adherence to the intervention. It is known that higher levels of fatigue negatively affect a cancer survivors' QoL [5]. Exercise may reduce fatigue and consequently improve a cancer survivors' QoL [40]. Cancer survivors with higher levels of fatigue at baseline may have more room for reducing their fatigue, and consequently have larger improvements in global QoL.

We found no moderating effect of marital status. This is in contrast with the studies of Courneya et al. [13, 14], who found a larger effect of exercise during cancer treatment on QoL in unmarried cancer survivors with breast cancer or lymphoma than in their counterparts. It has been suggested that unmarried cancer survivors may have less social support at home than married cancer survivors and consequently benefit more from the social group effect of the intervention [41], resulting in larger improvements in global QoL [42]. In contrast with the previous mentioned studies, our intervention was followed by cancer survivors who were at least three months after treatment. Perhaps, social support from a partner may be more important during treatment than after treatment. Cancer survivors who participated in our group-based rehabilitation program reported the support of fellow cancer survivors and the sharing of experiences to be an important part of the rehabilitation [43]. It should also be noted that only 10% in the WLC were single which may bias our findings. Future studies should investigate the moderating role of social support from a partner or fellow cancer survivors of the physical exercise effect on global QoL.

Strengths of the present study are the supervised, standardized and theory-based exercise interventions, the high attendance rates, and the low dropout rates. However, this study had some limitations. First, participants were not randomly assigned to the WLC group. Nevertheless, the groups were well balanced in baseline physical and psychological outcomes, and we adjusted for relevant sociodemographic and clinical variables in all analyses. Second, although the sample size was relatively large for an exercise trial among cancer survivors, the original study was not powered to investigate moderators of intervention effect. This study showed that the sample size should be at least 395 to be able to adequately conduct stratified analyses with a power of 80%. Therefore, our analyses of moderator effects should be interpreted as exploratory (hypothesis generating) post-hoc analyses. Identifying for whom and under what circumstances specific exercise interventions improve the QoL is an important step towards the development of personalized exercise interventions [44]. Future studies with large sample sizes are needed to confirm the moderator effects of being treated with radiotherapy or a combination chemo-radiotherapy and fatigue and to provide insight into whether people with different demographic, clinical and psychological characteristics indeed respond differently [11, 45].

In conclusion, this study suggests that the physical exercise effects immediately after intervention on global QoL were larger in cancer survivors who received radiotherapy, and in particularly those who received a combination of chemo-radiotherapy, and cancer survivors with higher baseline levels of fatigue compared to those who received no radiotherapy, no combination of chemo-radiotherapy, and had lower baseline fatigue levels, respectively. Future studies with larger sample sizes and thus more power are needed to confirm the moderator effects of treatment regimens and fatigue.

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Chapter 3

Mediators of exercise effects on HRQoL in cancer survivors after chemotherapy

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Medicine and science in sports and exercise, 2016; 48: 1859-65

Abstract

Purpose: We investigated the hypothesis that combined resistance and endurance exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and improving global quality of life (QoL) and physical function among cancer survivors who completed curative treatment including chemotherapy.

Methods: Cancer survivors were assigned to a 12-week exercise intervention (n=186) or a wait list control group (WLC, n=91). Data were collected at baseline and after 12 weeks. Path analyses using follow-up values adjusted for baseline values, age, and gender were conducted to test if the exercise effects on global QoL and physical function (European Organization Research and Treatment of Cancer-Quality of Life questionnaire-Core 30) were mediated by changes in cardiorespiratory fitness (peakVO2), hand-grip strength, lower body muscle function (30-second chair-stand test), and fatigue (Multidimensional Fatigue Inventory).

Results: Compared with WLC, exercise increased cardiorespiratory fitness (β= 1.7, 95% confidence interval (CI)= 0.9; 2.6 mL/kg/min) and reduced general (β= -1.0, 95% CI= -1.8; -0.2) and physical fatigue (β= -1.4, 95%CI= -2.2; -0.6). The exercise effect on physical fatigue was mediated by change in cardiorespiratory fitness (β= -0.1, 95% CI= -0.2; -0.0). Higher hand-grip strength was significantly associated with lower physical fatigue, and better lower body muscle function with lower physical and general fatigue. Lower general and physical fatigue were significantly associated with higher global QoL (β= -1.7, 95% CI= -2.2; -1.1 and β= -1.7, 95% CI= -2.3; -1.2, respectively), and physical function (β= -1.0, 95% CI= -1.3; -0.7 and β= -1.1, 95% CI= -1.5; -0.8, respectively). The models explained 44-61% of the variance in global QoL and physical function.

Conclusion: Beneficial effects of exercise on global QoL and physical function in cancer survivors were mediated by increased cardiorespiratory fitness, and subsequent reductions in fatigue.

Introduction

Recent systematic reviews and meta-analyses showed beneficial effects of exercise interventions on physical fitness, fatigue, and health-related quality of life (HRQoL) in cancer survivors [1-3]. However, reported effect sizes were small to moderate. To improve the effectiveness of exercise, it is important to gain more insight into the mechanisms by which an exercise intervention achieves its effect. Mediators may help identify effective intervention components. By keeping effective intervention components and by removing ineffective ones, the cost-effectiveness and participant burden of the interventions can be improved [4]. Furthermore, identification of mediators may support in the building and refining of intervention theory [5]. It is hypothesized that physical inactivity induces muscle catabolism and causes further detraining, which may result in a self-perpetuating detraining state with easily induced fatigue. Physical exercise may break this self-perpetuating cycle by improving physical fitness, and consequently reducing fatigue and improving HRQoL [6, 7].

Few previous studies investigated mediators of exercise effects on HRQoL in cancer survivors. They showed that the association between improved cardiorespiratory fitness and improved HRQoL was mediated by fatigue [8-11]. In a randomized controlled trial (RCT) among 57 prostate cancer survivors, Buffart et al. [8] showed that upper body muscle strength and walking speed mediated the effects of a 12-week combined resistance and endurance exercise intervention on physical health and that fatigue and walking speed mediated the effects on general health. Lower body muscle strength also mediated the effects of resistance and endurance exercise on global QoL and physical function in older long-term prostate cancer survivors. However, no mediating effects were found for cardiorespiratory fitness and fatigue [12].

To further build the knowledge of mechanisms underlying the exercise intervention effect on HRQoL, we tested the hypothesis that a combination of resistance and endurance exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue, and improving global QoL and physical function [13]. To test this hypothesis, we used data from the Resistance and Endurance exercise After ChemoTherapy (REACT) study [14, 15], that was conducted in a large group of cancer survivors (n=277) who had recently completed treatment with

curative intent, including chemotherapy.

Materials and methods

Patient recruitment and allocation

The REACT study was a multicenter RCT which evaluated the effectiveness of a 12-week high intensity exercise program (HI) and a low-to-moderate intensity (LMI) exercise program compared to a wait list control (WLC) group on physical fitness, fatigue, and HRQoL [14, 15]. A detailed description of the study procedures has been published previously [14, 15]. The medical ethics committees of the VU University Medical Centre and the local ethical boards of the participating hospitals had approved the study and written informed consent was obtained from all cancer survivors prior to participation [14, 15].

Cancer survivors were eligible for the study if they were aged ≥18 years, were treated for histologically confirmed breast, colon, ovarian, lymphatic, cervical or testicular cancer, had completed primary cancer treatment with curative intent including chemotherapy, and had no indication for recurrent or progressive disease [14, 15]. Cancer survivors were not eligible for the study if they were unable to perform basic activities of daily life, had cognitive disorders or severe emotional instability, had other serious diseases that might hamper the capacity of carrying out high intensity exercise (e.g., severe heart failure), or were unable to understand and read Dutch [14, 15].

Cancer survivors were recruited between 2011 and 2013 from 9 hospitals in the Netherlands. Baseline measurements were performed 4-6 weeks after completion of primary cancer treatment. After baseline measurements, participants were stratified by cancer type and hospital, and were randomly assigned into one of the three study arms. Both HI and LMI exercise groups started with their 12-weeks exercise program. Participants from the WLC group were offered the intervention, that they were randomly allocated to, after 12 weeks.

In total, 277 cancer survivors (response rate 37%) participated in the study. We previously reported that both HI and LMI exercise were able to increase cardiorespiratory fitness, reduce fatigue, and improve quality of life and physical

function compared with WLC [15]. The current analyses examine the mechanisms underlying the intervention effects on global QOL and physical function. Because we assumed that the intervention effects follow the same path as proposed in the hypothesized model, and to increase statistical power, we combined both intervention groups into one group. Therefore, 186 cancer survivors were allocated to the exercise intervention and 91 to the WLC group. Measurements were performed at baseline and after 12 weeks.

Interventions

A detailed description of the exercise interventions has been published elsewhere [14, 15]. In short, the exercise interventions took place twice a week for 12 weeks and were identical with respect to exercise type, frequencies and durations, and differed only in intensity. Resistance exercises included vertical row, leg press, bench press, pull over, abdominal crunch and lunges, and these were performed at 70-85% of 1 repetition maximum (1-RM) in the HI exercise group and at 40-55% of 1-RM in the LMI exercise group. Aerobic interval training aimed to improve cardiorespiratory endurance and included 2 times 8 minutes of cycling in the first 4 weeks, with an alternating workload of 30% and 65% of the maximal short exercise capacity (estimated by the steep ramp test [16]) in the HI exercise group and 30% and 45% in the LMI exercise group. From the fifth week onwards, an additional aerobic interval session was included in exchange for 8 minutes cycling. This interval session consisted of 3 times 5 minutes cycling at constant workload, with 1 minute rest between each bout. The constant workload was defined by means of heart rate reserve based on the Karvonen formula [17], and was at least 80% of heart rate reserve for HI exercise and 40-50% for LMI exercise. On average, 70% of the cancer survivors had high adherence rates, defined as attending 80% of the prescribed supervised exercise sessions [15].

Outcome measure

HRQoL was measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [18], with higher scores representing a higher global QoL and better function. We used the global QoL and physical

function scales for further analyses.

Potential mediators

Cardiorespiratory fitness was measured with a maximal exercise test on an electronically braked cycle ergometer according to a ramp protocol in which the resistance gradually increased every 6 seconds, aiming to achieve the maximum peak oxygen uptake (peakVO2) within 8 to 12 minutes [19, 20]. PeakVO2 was defined as the highest VO2 value averaged over a 15-second interval within the last minute of exercise, and was expressed in mL/kg/min.

Hand-grip strength was assessed with a JAMAR hand-grip dynamometer [21], and was expressed in kilograms. The mean score of the 3 attempts with the dominant hand was used in the statistical analyses. We used the 30-second chair-stand test as a measure for lower body muscle function [22]. The total number of times participants raised to a full stand in 30 seconds was used in the statistical analyses.

Self-reported fatigue was measured with the Multidimensional Fatigue Inventory [23]. We used the general and physical fatigue subscales for further analyses, with higher scores indicating higher levels of fatigue.

Covariates

Demographic characteristics were collected at baseline with a self-reported questionnaire and included age, gender, education level, marital status, and smoking. We categorized education level into low (elementary and lower vocational education), medium (secondary and secondary vocational education), and high (higher vocational and university education). Clinical characteristics were collected from medical records and included cancer type, stage of disease, and treatment history (i.e., radiation therapy, immunotherapy, hormonal therapy and/or surgery) [15].

Statistical analyses

Baseline characteristics and pre- and post-intervention values of the outcome assessments are presented as means and standard deviations (SD), or as numbers and percentages. To test the hypothesis that exercise improves physical fitness (i.e., cardiorespiratory fitness, hand-grip strength, and lower body muscle function), which is associated with lower general and physical fatigue and higher global QoL and physical function (Figure 3.1), we conducted path analyses using maximum likelihood estimation with MPlus. Path analysis allows the simultaneous assessment of multiple regression equations [24]. Four separate path models were built using follow-up values of the mediators and outcome variables, adjusting for their baseline values, age and gender: 1) physical fitness and general fatigue as mediators in the intervention effects on global QoL; 2) physical fitness and physical fatigue as mediators in the intervention effect on global QoL; 3) physical fitness and general fatigue as mediators in the intervention effects on physical function; and 4) physical fitness and physical fatigue as mediators in the intervention effect on physical function. Bootstrapping techniques were applied to calculate the 95% confidence interval (CI) around the estimates of the direct and indirect effects using 10,000 bootstrap samples. The model fit was evaluated using the root mean square error of approximation (RMSEA), with values below 0.05 for good fit (acceptable fit: 0.05-0.09), the Comparative Fit Index (CFI), and the Tucker-Lewis (TLI) index with values above 0.95 as good fit (adequate fit: >0.90) [25]. These tests were used because they are least sensitive to sample size, and provide unbiased and consistent model specifications [26]. The path analyses were based on complete cases.

Because we pooled data from the HI and LMI exercise groups including a heterogeneous group of cancer survivors, we conducted sensitivity analyses to test whether the mediator effects were similar between the two intervention groups and between survivors of breast cancer (n=181) or other (n=96) cancer types.

Results

The mean age of the participants in the exercise group was 53.6 (SD=11.1) years, 81% was female, and 67% was diagnosed with breast cancer (Table 3.1). Participants in the WLC group were on average 53.5 (SD=10.9) years old, 78% was female, and

63% was diagnosed with breast cancer. Descriptive values of all outcomes for the exercise and WLC groups at pre-intervention and post- intervention are presented in Table 3.2.

Table 3.1. Sociodemographic and clinical characteristics of the exercise and wait-list control group (n=277)

	Exercise group (n=186)	**Wait-list control group (n=91)**
Sociodemographic		
Age, mean (SD) years	53.6 (11.1)	53.5 (10.9)
Gender, n (%) male	35 (19)	20 (22)
Married/living together, n (%)	160 (86)	72 (79)
Education		
Low	31 (17)	16 (18)
Medium	80 (44)	42 (46)
High	72 (39)	33 (36)
Smoking, n (%)	12 (7)	5 (6)
Clinical		
Type of cancer, n (%)		
Breast	124 (67)	57 (63)
Colon	34 (18)	15 (17)
Ovarian	7 (4)	5 (6)
Lymphatic	18 (10)	8 (9)
Cervical	2 (1)	2 (2)
Testicular	1 (1)	4 (4)
Stage of cancer, n (%)		
Stage 1-2	125 (67)	62 (68)
Stage 3-4	61 (33)	29 (32)
Type of treatment, n (%)		
Surgery only	170 (91)	80 (88)
Radiotherapy only	87 (47)	48 (53)
Surgery and radiotherapy	80 (43)	46 (51)
Immunotherapy	41 (22)	18 (20)
Hormone therapy	85 (46)	43 (47)

Abbreviation: SD = standard deviation

We found a significant beneficial effect of exercise on cardiorespiratory fitness, but not on hand-grip strength or lower body muscle function (Figure 3.1, Table 3.3). In addition, higher cardiorespiratory fitness was significantly associated with lower physical fatigue (Figure 3.1b and 3.1d), but not with general fatigue (Figure 3.1a and 3.1c). Better lower body muscle function test was significantly associated with lower general and physical fatigue. Higher hand-grip strength was significantly associated with lower physical fatigue (Figure 3.1b and 3.1d). We also found a direct effect of the exercise on general and physical fatigue.

Both lower general and physical fatigue were significantly associated with higher global QoL and physical function. Higher cardiorespiratory fitness was significantly associated with higher physical function (Figure 3.1c and 3.1d), but not with global QoL (Figure 3.1a and 3.1b).

The paths explained 44-61% of the total variance in global QoL or physical function and the models had an adequate fit (RMSEA <0.08; CFI >0.98; TLI >0.95, Figure 3.1). Sensitivity analyses showed larger effects on global QoL for HI compared to LMI exercise and for survivors of breast cancer compared to survivors of other cancer types. Other paths were comparable across subgroups.

Table 3.2. Pre- and post-intervention values of mediator and outcome variables in the exercise and wait list control groups

	Exercise group		**Wait-list control group**	
	Pre-test mean (SD)	Post-test mean (SD)	Pre-test mean (SD)	Post-test mean (SD)
Health-related quality of life [a]				
Global quality of life	73.2 (16.2)	80.9 (14.9)	71.0 (16.5)	75.3 (15.4)
Physical function	82.5 (13.0)	88.8 (9.8)	80.2 (15.4)	84.1 (13.1)
Fatigue [b]				
General fatigue	12.7 (3.9)	10.1 (3.4)	12.7 (4.2)	11.3 (4.1)
Physical fatigue	12.6 (3.9)	9.2 (3.4)	13.2 (4.0)	11.2 (3.9)
Cardiorespiratory fitness [c]				
peakVO_2 (ml/kg/min)	22.1 (6.2)	26.0 (7.1)	21.5 (5.5)	23.8 (5.9)

Table 3.2 (continued)

	Exercise group		Wait-list control group	
	Pre-test mean (SD)	Post-test mean (SD)	Pre-test mean (SD)	Post-test mean (SD)
Hand-grip strength [d]				
Hand-grip strength (kg)	32.7 (9.7)	34.6 (10.1)	33.5 (9.5)	35.5 (10.6)
Lower body muscle function [e]				
Sit to stand (stands)	16.7 (4.0)	19.0 (4.8)	15.6 (3.6)	17.6 (3.9)

[a] Missing due to incomplete questionnaire (n=1); [b] Missing due to incomplete questionnaire (n=1); [c] Missing due to technical problems (n=5), musculoskeletal problems (n=1), or discomfort (n=6). Eight percent did not achieve the objective end criteria of respiratory exchange ratio ≥1.10 at baseline and follow-up; [d] Missing due to technical problems (n=3) or musculoskeletal problems (n=2); [e] Missing due to musculoskeletal problems (n=2). Abbreviations: Kg, kilograms; ml, milliliters; min, minutes; peakVO_2, maximum peak oxygen uptake; SD, standard deviation

Discussion

The current study found support for the hypothesis that a combined resistance and endurance exercise intervention improves cardiorespiratory fitness, which is associated with lower physical fatigue, and higher global QoL and physical function. Further, we found that higher hand-grip strength was significantly associated with lower physical fatigue, and better lower body muscle function with lower general and physical fatigue.

We previously reported beneficial effects of the exercise intervention on cardiorespiratory fitness, fatigue, and HRQoL [15], which supports previous reviews and meta-analyses [1, 2, 27]. The current study further elucidates these findings by providing insight into the mechanisms underlying the beneficial effects of resistance and endurance exercise on HRQoL.

Our finding that improved cardiorespiratory fitness mediated the exercise effects on physical fatigue, but not on general fatigue indicates that improving cardiorespiratory fitness is an important intervention strategy to reduce physical fatigue. The lack of mediating effect of improved cardiorespiratory fitness on

Table 3.3. Unstandardized regression coefficients of the total and indirect effects and their 95% confidence intervals (CI) of the exercise intervention effect on global quality of life (QoL) and physical function, with cardiorespiratory fitness, hand-grip strength, lower body muscle function, and fatigue (either general or physical) as potential mediators

Model results	General fatigue Estimate (95% CI)	Physical fatigue Estimate (95% CI)
Global QoL		
Effect from intervention on fatigue		
Total effect	-1.1 (-1.9; -0.3)*	-1.6 (-2.4; -0.8)*
Total indirect effect	-0.1 (-0.3; 0.0)	-0.2 (-0.4; -0.1)*
Specific indirect effect via:		
Cardiorespiratory fitness	-0.1 (-0.2; 0.0)	-0.2 (-0.4; -0.1)*
Hand-grip strength	0.0 (-0.0; 0.1)	-0.0 (-0.1; 0.1)
Lower body muscle function	-0.0 (-0.2; 0.0)	-0.0 (-0.2; 0.0)
Effect from intervention on global QoL		
Total effect	4.5 (1.2; 7.8)*	4.1 (0.8; 7.4)*
Total indirect effect	2.2 (0.8; 3.8)*	3.0 (1.5; 4.8)*
Specific indirect effect via:		
Fatigue	1.6 (0.4; 3.1)*	2.4 (1.1; 4.2)*
Cardiorespiratory fitness	0.3 (-0.1; 0.9)	0.1 (-0.3; 0.7)
Hand-grip strength	-0.0 (-0.2; 0.1)	0.0 (-0.1; 0.2)
Lower body muscle function	0.1 (-0.1; 0.6)	0.1 (-0.1; 0.6)
Cardiorespiratory fitness and fatigue	0.1 (-0.1; 0.4)	0.3 (0.1; 0.7)*
Hand-grip strength and fatigue	-0.0 (-0.1; 0.1)	0.0 (-0.2; 0.1)
Lower body muscle function and fatigue	0.1 (-0.0; 0.3)	0.1 (-0.0; 0.3)
Physical function		
Effect from intervention on fatigue		
Total	-1.1 (-1.9; -0.3)*	-1.6 (-2.4; -0.8)*
Total indirect	-0.1 (-0.3; 0.0)	-0.2 (-0.4; -0.1)*
Specific indirect		
Cardiorespiratory fitness	-0.1 (-0.2; 0.0)	-0.2 (-0.4; -0.1)*
Hand-grip strength	0.0 (-0.0; 0.1)	-0.0 (-0.1; 0.1)
Lower body muscle function	-0.0 (-0.2; 0.0)	-0.0 (-0.2; 0.0)

Table 3.3 (continued)

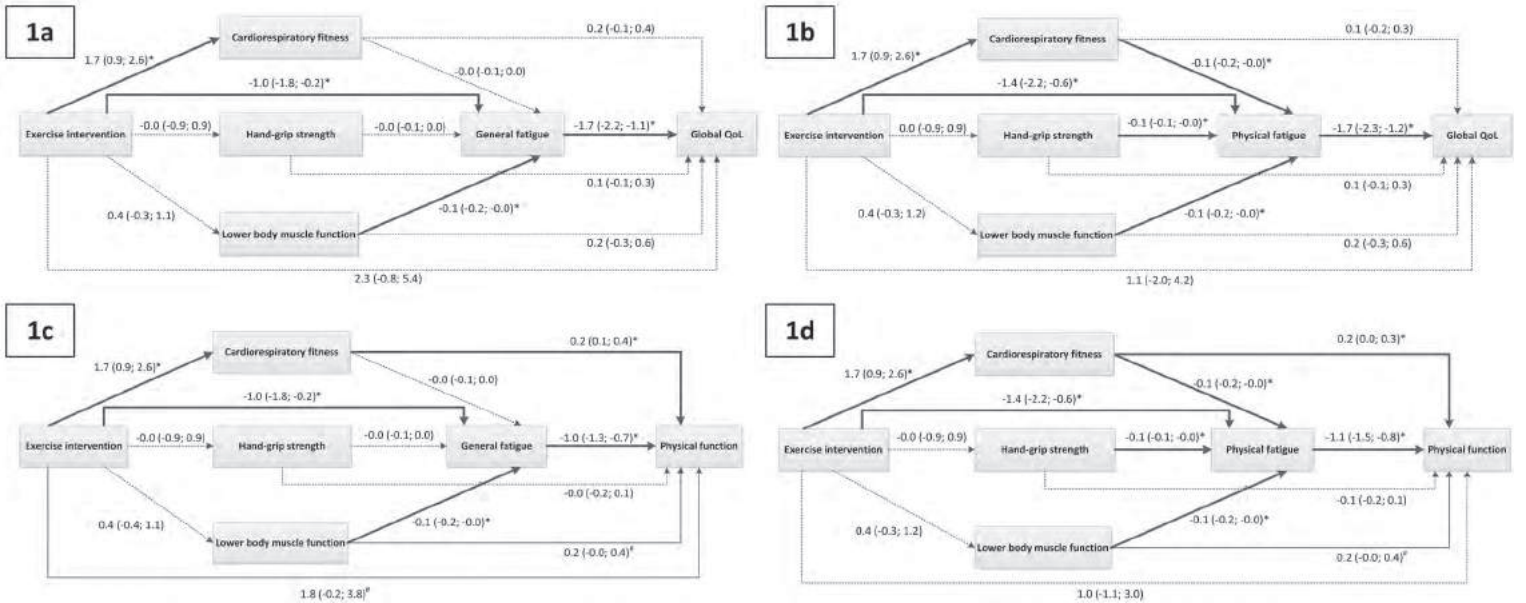
Model results	General fatigue Estimate (95% CI)	Physical fatigue Estimate (95% CI)
Effect from intervention on physical function		
Total effect	3.3 (1.2; 5.5)*	3.2 (0.9; 5.3)*
Total indirect effect	1.5 (0.7; 2.6)*	2.2 (1.2; 3.5)*
Specific indirect effect via:		
Fatigue	0.9 (0.2; 1.9)*	1.6 (0.7; 2.7)*
Cardiorespiratory fitness	0.4 (0.1; 0.9)*	0.3 (0.0; 0.7)#
Hand-grip strength	0.0 (-0.1; 0.1)	-0.0 (-0.1; 0.1)
Lower body muscle function	0.1 (-0.0; 0.3)	0.1 (-0.0; 0.4)
Cardiorespiratory fitness and fatigue	0.1 (-0.0; 0.2)	0.2 (0.1; 0.5)*
Hand-grip strength and fatigue	-0.0 (-0.1; 0.0)	0.0 (-0.1; 0.1)
Lower body muscle function and fatigue	0.0 (-0.0; 0.2)	0.0 (-0.0; 0.2)

Abbreviations: SE, standard error. Path analyses using maximum likelihood estimation with MPlus adjusted for baseline scores of the mediator, age and gender; * $p<0.05$; # $0.05 \leq p<0.10$

general fatigue is in line with previous findings in prostate [8] and breast cancer survivors [28]. This may be explained by the fact that general fatigue does not only include physical aspects, but also mental aspects, which are perhaps more likely influenced by concepts other than or additional to cardiorespiratory fitness. It is possible that psychological factors such as depression and anxiety may mediate exercise effects on general fatigue [29]. Furthermore, exercise effects on fatigue could also be mediated by biological factors (e.g., improved body composition, and increased pro-inflammatory cytokines [30], or other psychosocial factors, such as reduced sleep quality, mastery, and self-efficacy [9, 29]. These factors may also explain the direct beneficial effect of exercise on general fatigue in the current study as well as in a previous study [9].

In line with findings from previous studies [8, 28], we found that higher hand-grip strength and better lower body muscle function was significantly associated with lower fatigue. We further found that better lower body muscle function tended to be associated with higher physical function. This indicates that muscle strength and function might be important intervention targets when aiming to reduce fatigue and improving physical function. However, due to the lack of a significant intervention effect on hand-grip strength and 30-second chair-stand

Figure 3.1. Path models showing cardiorespiratory fitness, hand-grip strength, lower body muscle function, and fatigue as hypothesized mediators of the effect of the exercise intervention on global quality of life (QoL) and physical function



Note: Numbers represent unstandardized regression coefficients and their 95% confidence intervals (CI). Dotted lines represent non-significant associations, solid lines represent significant associations. Abbreviations: CFI, Comparative Fit Index; RMSEA, Root Mean Square Error of Approximation; TLI, Tucker Lewis index. [a] The model fitted the data: RMSEA= 0.067, 90% CI= 0.041; 0.093, CFI= 0.981, TLI= 0.958. Explained total variance in global QoL = 0.4; [b] The model fitted the data: RMSEA= 0.073, 90% CI= 0.048; 0.098, CFI= 0.977, TLI= 0.950. Explained total variance in global QoL = 0.4; [c] The model fitted the data: RMSEA= 0.065, 90% CI= 0.039; 0.091, CFI= 0.983, TLI= 0.963. Explained total variance in physical function = 0.6; [d] The model fitted the data: RMSEA= 0.080, 90% CI= 0.056; 0.105, CFI= 0.975, TLI= 0.945. Explained total variance in physical function = 0.6; * $p < 0.05$; # $0.05 \leq p < 0.10$

test, we could not confirm that muscle strength and function mediated the exercise effects on fatigue and physical function. The lack of significant effects of exercise on muscle strength is in contrast with a previous meta-analysis [31] and a systematic review [32] summarizing the effects of exercise on muscle strength, and may be related to our choice of instruments used to assess the outcomes. Despite being valid and reliable measures of hand-grip strength [25] and lower body muscle function [33], they may have been less sensitive to detect exercise-induced changes. Future studies are needed to clarify the mediating role of muscle strength in the exercise-intervention effect on fatigue and physical function.

We further found that the effects of exercise on global QoL can be explained by reduced fatigue, which supports findings from previous studies [8-11]. In older long term prostate cancer survivors, lower general fatigue was associated with higher global QoL [12]. However, in this study lower general fatigue was not a mediator of the exercise effect [12]. Furthermore, our results demonstrate that the effects of exercise on physical function can be explained by reduced general and physical fatigue. This is in contrast to a study in prostate cancer survivors [8], which reported that general fatigue mediated the effects of exercise on global QoL but not on physical function. This lack of mediating effects of general fatigue on global QoL or physical function in these studies may be related to the lower baseline values of fatigue, leaving less room for improvement. In contrast, our study clearly suggests that reducing fatigue can be important to improve global QoL and physical function, and that exercise is an effective strategy to do so.

In addition to its effect via fatigue, we also found a direct association between improved cardiorespiratory fitness and improved physical function. The mediating role of cardiorespiratory fitness in the intervention effect on physical function was not found in studies among prostate cancer survivors [8, 12]. Differences in mediating effects may be related to differences in study population, or to the type of instrument used to measure cardiorespiratory fitness [15]. Instead of the submaximal exercise test, the current study used a gold standard maximum exercise test to assess cardiorespiratory fitness, which may be more sensitive to detect changes and less prone to measurement error [34]. Baseline peakVO2 values of our population were low compared to normative values [35], which may interfere with daily life functioning [36]. Our study showed that this can be (partially) counteracted by a training program of 12 weeks that improves cardiorespiratory

fitness.

The strengths of the present study are the examination of mediators in a well-designed RCT with a relatively large sample size, the use of valid and reliable instruments to assess outcome measures, and the use of path analyses enabling the simultaneous evaluation of multiple mediators [37]. However, despite the use of an RCT design, one should still be cautious when making inferences about causality, because the mediator and outcome variables were measured at the same time [24]. Consequently, we studied associations rather than temporal relationships between these variables, and the reverse – that higher global QoL and physical function were associated with lower levels of fatigue – may also be true. However, fatigue was found to be the strongest predictor of HRQoL and physical function [38], supporting the direction of the association studied. Another limitation is the use of indirect measures to assess muscle strength. Both hand-grip strength and 30-second chair-stand test are valid and reliable measures to assess hand-grip strength [25] and lower body muscle function [33]. In addition, the use of (indirect) 1-RM tests would introduce learning bias in the intervention group because these tests were included as part of the intervention. However, hand-grip strength and 30-second chair-stand test may not have been sensitive enough to detect exercise-induced changes. Finally, to increase statistical power, and because we hypothesized that the intervention effects had similar mechanisms underlying beneficial effects on global QoL and physical function, we pooled the data from both intervention groups. Our sensitivity analyses indicated that paths were comparable across subgroups, except for the intervention effect on global QoL, which was larger for HI than LMI exercise and for survivors of breast cancer compared to other cancer types [15]. As a result of pooling, we were unable to distinguish differences in strengths of mediator effects between HI and LMI exercise.

Current results contribute to the understanding of the mechanisms by which a resistance and endurance exercise intervention achieves its effect on global QoL and physical function in cancer survivors. These results will help to further tailor interventions to the desired outcome. Supported by previous studies showing beneficial effects of exercise on cardiorespiratory fitness [1], it is recommended to improve cardiorespiratory fitness in order to reduce fatigue. Furthermore, reducing fatigue helps to improve the cancer survivors' global QoL and physical function.

In conclusion, this study found support for the hypothesis that exercise increases cardiorespiratory fitness, and consequently reduces physical fatigue and improves global QoL and physical function in cancer survivors shortly after completion of primary cancer treatment. Improving cardiorespiratory fitness could therefore be an important intervention target to reduce fatigue and to improve cancer survivors' global QoL and physical function.

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Chapter 4

Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS); Rationale and design for meta-analyses of individual patient data of randomized controlled trials evaluating the effect of exercise and psychosocial interventions on health-related quality of life in cancer survivors

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Systematic reviews, 2013; 2: 75

Abstract

Background: Effective interventions to improve quality of life of cancer survivors are essential. Numerous randomized controlled trials have evaluated the effects of physical activity, exercise or psychosocial interventions on health-related quality of life of cancer survivors, with generally small sample sizes and modest effects. Better targeted interventions may result in larger effects. To realize such targeted interventions, we must determine which presently available interventions work for which patients, and what the underlying mechanisms are; i.e. the moderators and mediators of physical activity, exercise and psychosocial interventions. Individual patient data meta-analysis has been described as the 'gold standard' of systematic review methodology. Instead of extracting aggregate data from study reports or from authors, the original research data are sought directly from the investigators. Individual patient data meta-analyses allow for adequate statistical analysis of intervention effects and moderators of such effects. Here, we report the rationale and design of the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) Consortium. The primary aim of POLARIS is to: 1) conduct meta-analyses based on individual patient data to evaluate the effect of physical activity, exercise and psychosocial interventions on the health-related quality of life of cancer survivors; 2) identify important sociodemographic, clinical, personal, or intervention-related moderators of the effect; and 3) build and validate clinical prediction models identifying the most relevant predictors of intervention success.

Methods: We will invite investigators of randomized controlled trials evaluating the effects of physical activity, exercise or psychosocial interventions on health-related quality of life compared with a wait-list, usual care or attention control group among adult cancer survivors to join the POLARIS consortium and share their data for pooled analyses to address the proposed aims. We are in the process of identifying eligible randomized controlled trials through literature searches in four databases. To date, we have identified 132 eligible and unique trials.

Discussion: The POLARIS consortium will conduct the first individual patient data meta-analyses in order to generate evidence essential to targeting physical activity, exercise and psychosocial programs to the individual survivor's characteristics, capabilities, and preferences.

Background

Worldwide, it has been estimated that there were about 12.7 million cancer cases and 7.6 million cancer deaths in 2008 [1]. Due to advances in early detection and treatment, survival after cancer diagnosis has improved substantially. Nevertheless, for most patients, cancer survivorship (i.e. from the time of diagnosis [2]) is associated with significant adverse physical and psychosocial problems. These include fatigue, pain, increased risk of anxiety and depression, reduced physical fitness and physical function [3, 4], and impaired health-related quality of life (HRQoL) [5, 6]. The term HRQoL denotes a range of health outcomes and effects, including physical, mental and social functioning, symptom burden and perceived health status [7, 8].

A range of physical activity, exercise and psychosocial interventions targeting HRQoL outcomes in cancer survivors have been developed and evaluated. Many of these interventions have been studied in the context of a randomized controlled trial (RCT). In general, meta-analyses of these RCTs have yielded significant, positive results, although the mean effect sizes tend be small to moderate [9-12].

One possible explanation for the lack of larger effect sizes is that these interventions are typically offered to a heterogeneous group of cancer survivors and are not sufficiently targeted to specific patients. Also, the use of different HRQoL definitions and assessment tools undoubtedly contributes to the relatively wide range of findings regarding the strength of intervention effects. Finally, determinants of HRQoL may vary between individuals and change over time. Thus, similar to developments in personalized primary cancer therapy, physical activity, exercise and psychosocial interventions should be optimally targeted to the individual's characteristics, health state, needs, preferences, capabilities and opportunities.

To be able to shift from a 'one-size-fits-all' approach to more personalized physical activity, exercise and psychosocial interventions, it is essential to know *which* existing programs work, for *whom*, and under *what* circumstances, i.e., to identify important moderators of intervention effects. Moderators identify which patients might be most responsive to the intervention, providing valuable information for decision-making [13]. The few published studies of potential moderators of the effects of exercise and psychosocial interventions have suggested that sociodemographic, clinical and personal factors such as age, marital status, disease stage, type of treatment, and baseline functioning may help to understand

differences in responses to physical activity, exercise and psychosocial interventions [14-18]. However, most of these earlier reports were based on single studies that were not designed or powered to analyze moderating effects and conduct subsequent stratified analyses.

To further improve the effectiveness and efficiency of physical activity, exercise and psychosocial interventions, it is also important to identify and subsequently target critical intervention components (i.e. mediators of intervention effect). For example, previous studies have shown that fatigue and psychological distress may mediate the association between physical activity or exercise and HRQoL [19, 20]. However, such studies are scarce.

An individual patient data (IPD) meta-analysis has been suggested as the preferred method to identify moderators of intervention effects [21]. In contrast to meta-regression analyses of aggregated data used in study-level meta-analyses, an IPD meta-analysis allows for testing of interactions to evaluate whether patient and setting characteristics are related significantly to treatment effects [21]. Other key benefits of an IPD meta-analysis include the larger number of data points, facilitating more powerful statistical conclusions based on careful evaluation of modeling assumptions and accounting for missing data at the individual patient level, the ability to standardize analytical techniques, inclusion criteria and outcome definitions across studies, the possibility of identifying relevant subgroups, and the ability to develop and test new and existing prediction models [22-24].

In this paper, we describe the protocol of the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) project. The primary objectives of the POLARIS project are to: 1) conduct IPD meta-analyses to evaluate the effects of physical activity, exercise and psychosocial interventions on the HRQoL of cancer survivors; 2) identify those sociodemographic, clinical and personal characteristics, and intervention types and circumstances that moderate the effects of physical activity, exercise and psychosocial interventions; and 3) build and validate clinical prediction models that identify the most relevant predictors of intervention success (i.e. improvement in HRQoL). The secondary aim of the project is to explore which variables mediate the effect of physical activity, exercise and psychosocial interventions on HRQoL.

To our knowledge, this is the first IPD meta-analysis conducted on the effects

of physical activity, exercise and psychosocial interventions on HRQoL of cancer survivors. For the POLARIS project, we have established a consortium that will be expanded to include as many investigators as possible who have conducted RCTs evaluating the effects of physical activity, exercise and/or psychosocial interventions on HRQoL.

Methods

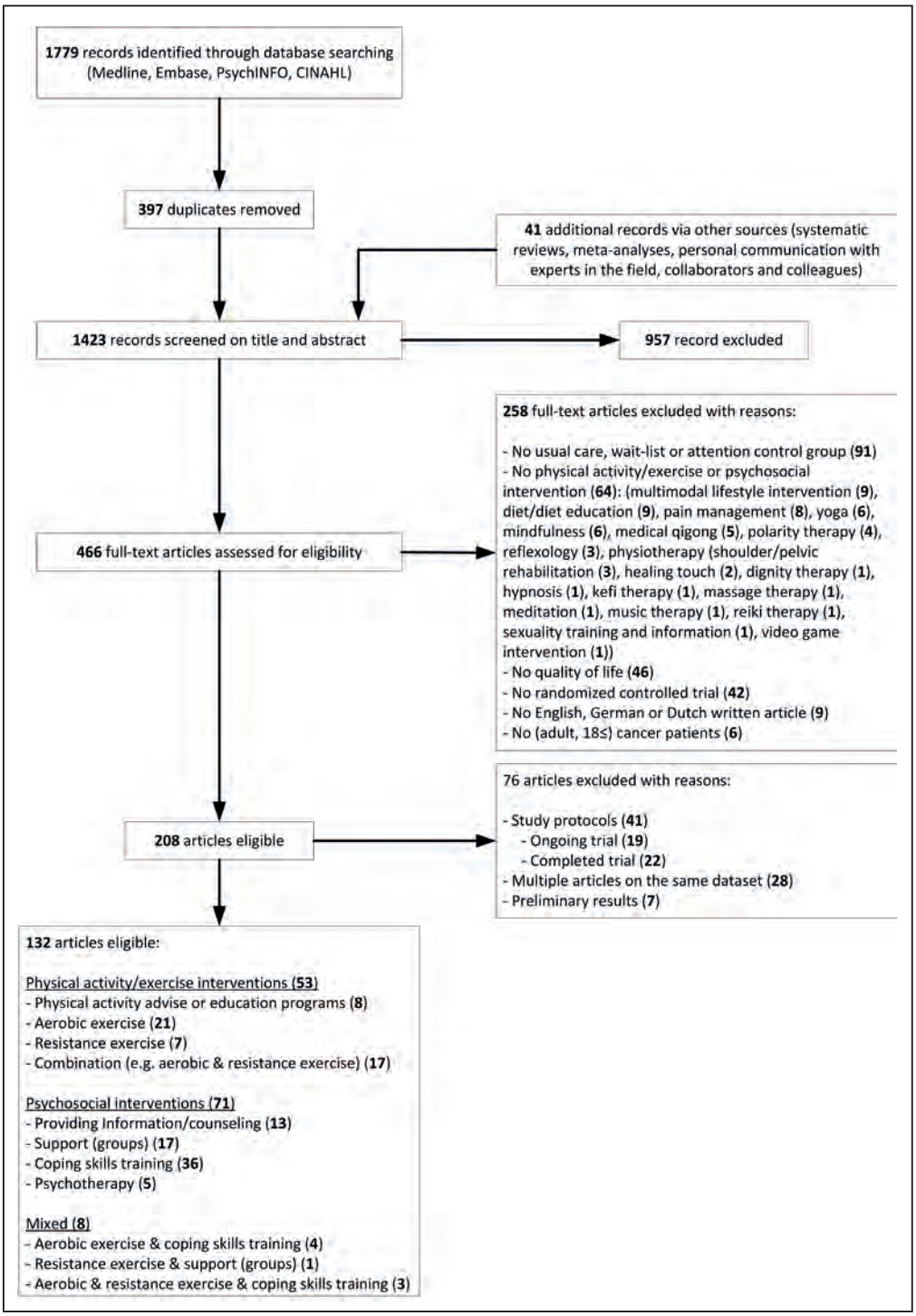
Inclusion and exclusion criteria

For POLARIS, we will include RCTs conducted among adult cancer survivors in which the effects of physical activity, exercise or psychosocial interventions on HRQoL are evaluated in comparison to a wait-list, usual care or attention control group (Table 4.1). In addition, the RCTs should have approval of a Medical Ethics Committee as well as signed informed consent of each participant. Psychosocial interventions will be included if they fit into the framework proposed by Cunningham [25]. This framework classifies psychosocial interventions into five categories: 1) patient education; 2) social support; 3) coping skills training; 4) psychotherapy; and 5) spiritual/existential therapy. In order to reduce the heterogeneity among the interventions to be included, we will initially exclude studies focusing on spiritual or existential therapy, yoga, mindfulness, pain management, diet or multimodal lifestyle interventions (e.g., physical activity and diet combined).

Identification and selection of studies

We used several strategies to identify eligible studies, including literature searches and personal communication with experts in the field, collaborators and colleagues. Electronic databases of PubMed, EMBASE, PsycINFO, and CINAHL were searched, without language restrictions, to obtain an overview of studies published. Because of language barriers, for the time being we have only included articles published in English, German or Dutch. We used medical subject heading (MESH) and text words related to cancer, physical activity, exercise, psychosocial therapy, (health-related) quality of life, randomized controlled trials and adult. Detailed search strategies of all databases are available on request (See Appendix for the strategy in PubMed).

Figure 4.1. Flow chart of study selection



We identified additional records by examining other sources (i.e. systematic reviews, meta-analyses, personal communication with experts in the field, collaborators and colleagues) until no further studies were found.

To date, based on the search through September 2012, we have identified a total of 1779 records through database searching, and an additional 41 records through other sources (Figure 4.1). After removing duplicates, we screened 1423 records on title and abstract, of which 957 were out of scope. We assessed full text articles of 466 records for eligibility, of which 208 met the inclusion criteria. We excluded 76 of these articles because they were descriptions of a study protocol, or were multiple publications from the same trial. Finally, 132 unique RCTs met our inclusion criteria (Table 4.1). We will invite the principal investigators of all 132 studies to participate in the POLARIS consortium. This will involve sharing their trial data and participating in analyses and manuscript preparation (see below).

Table 4.1. Study inclusion criteria

1.	Study design	Randomized controlled trial	
2.	Patients	Adult (≥18 years) cancer survivors	
3.	Intervention	Physical activity, exercise or psychosocial intervention	
		Physical activity/ exercise intervention	*Psychosocial interventions* [1]
		Physical activity advise or education	Providing information/counseling
		Aerobic exercise	Support groups
		Resistance exercise	Coping skills training
		Combination	Psychotherapy
4.	Control group	Wait-list, usual care or attention control	
5.	Outcome	Health-related quality of life included as primary or secondary outcome measure	

[1] According to the Framework proposed by Cunningham [25]

Core data set and variables

The main outcome measures are overall HRQoL and specific HRQoL domains (e.g., physical, psychological, functional, and social well-being) measured such

multidimensional questionnaires as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) [26], the Short Form-36 Item Health Survey (SF-36) [27] and its abbreviated verison, the SF-12 [28], the Functional Assessment of Chronic Illness Therapy (FACIT) [29], the Functional Assessment of Cancer Therapy (FACT) [30], and the EuroQol 5D (EQ5D) [31]. Other patient-related outcomes of interest and baseline characteristics include physical activity (measured by self-report and/or objective assessment instruments) and physical fitness (e.g. peak oxygen uptake (VO_2)), body composition, symptoms (e.g., fatigue) and psychosocial variables including anxiety, depression, distress, mood, self-esteem, sleep quality and social support (Table 4.2). No outcome measure will be excluded a priori.

Relevant baseline characteristics to be included in the POLARIS database include the patient and center identifier, important sociodemographic and clinical variables, as well as intervention characteristics (Table 4.2).

Table 4.2. Overview primary, secondary outcome and independent variables

Primary outcome measures	***Assessment Instrument***
Health-related quality of life	E.g. EORTC QLQ C30, FACIT, FACT, SF-36, SF-12, EQ5D.
Secondary outcome measures and independent variables	***Variable name***
Psychosocial factors	Fatigue, depression, anxiety, mood state, stress/distress, self-esteem, anger, sleep quality, social support.
Physical activity and fitness	Functional performance (e.g. 6 min walk test), muscle strength, aerobic fitness (e.g., peakVO_2), physical activity (objectively or by self-report).
Physical activity and fitness	Functional performance (e.g. 6 min walk test), muscle strength, aerobic fitness (e.g., peakVO_2), physical activity (objectively or by self-report).
Body composition	Height, weight, body mass index, fat mass, lean body mass, thickness of skin folds, body fat (in percentages), arm circumference, waist circumference, hip circumference, waist-hip ratio, bone mineral density.
Independent variables	
Baseline characteristics	Patient identifier, center identifier, date of diagnosis, time since diagnosis, date of randomization, and timing of intervention (pre/during/post intervention or mixed timing).

Table 4.2 (continued)

Demographic variables	Age, gender, family income, employment status, level of education, marital status, ethnicity/race, smoking, alcohol use, menopausal status, performance status (e.g., Karnofsky Performance Scale).
Clinical characteristics	Cancer diagnosis (e.g. breast cancer), cancer staging and grading, TNM Classification of Malignant Tumors, oncologic history, recurrence of cancer, co-morbidities, treatment of co-morbidities, cancer-related pain, medication use, type of medication, type of treatment (e.g. chemo/radio/ hormone therapy), number of cycles, time since treatment, currently under treatment, complications during treatment, other treatments used (e.g. immunotherapy, stem cell transplantation).
Psychosocial intervention characteristics	Method of delivery (e.g. telephone support, face-to-face), intervention type (e.g. education, cognitive behavioral therapy, psychotherapeutic), intervention format (e.g. group, individual, couples, web-based), total number of sessions of the intervention, number of care providers involved in the intervention, profession of care providers involved in the intervention, training given to the care providers involved in the intervention, compliance.
Physical activity/exercise intervention characteristics	Intervention duration, exercise mode (e.g. resistance, endurance), exercise intensity, exercise frequency, exercise session duration, exercise supervision, compliance.

Abbreviations: EORTC QLQ C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ5D= EuroQoL 5D; FACIT= Functional Assessment of Chronic Illness Therapy; FACT= Functional Assessment of Cancer Therapy; peakVO2= peak oxygen consumption; SF-36= Short Form-36; SF-12= Short Form-12; TNM= tumor node metastasis.

Establishing the collaborative group

The POLARIS Steering Committee will send a letter of invitation to join the POLARIS consortium to the principal investigator of each study that is eligible for the POLARIS database. This (e)mail contains a short introduction to POLARIS, including the aim and inclusion criteria, and a short description of the POLARIS policy and procedures. If and when principal investigators express interest in joining the consortium and sharing their data, they are asked to provide more trial information and to describe which data they are willing to share with the POLARIS database. Further, the full

POLARIS policy and a data sharing agreement form will be sent to the principal investigator. Reasons for refusal will be recorded. After receiving the signed data sharing agreement form, a data transfer protocol will be sent with a suggested data-coding scheme allowing flexibility in the format to ensure convenience to all collaborators. Alternatively, if data management support is needed, the dataset may be transferred with the original coding scheme.

Data acquisition, collection and checking

We will ask study collaborators to supply raw data as outlined by the data request form. The data can be transferred in any electronic format (e.g., SPSS, SAS, and STATA). Data will be transferred using a password-protected encryption (e.g., AxCrypt). Once the original data file is received from the principal investigator, it will be transferred to SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) and the original data will be archived for backup purposes.

Before transferring the data to the POLARIS database, data sets must be anonymized by the original investigators (i.e., have all directly identifiable material, including name, address, postal code or medical record number removed). A unique patient identification number should be provided to facilitate communication and data queries.

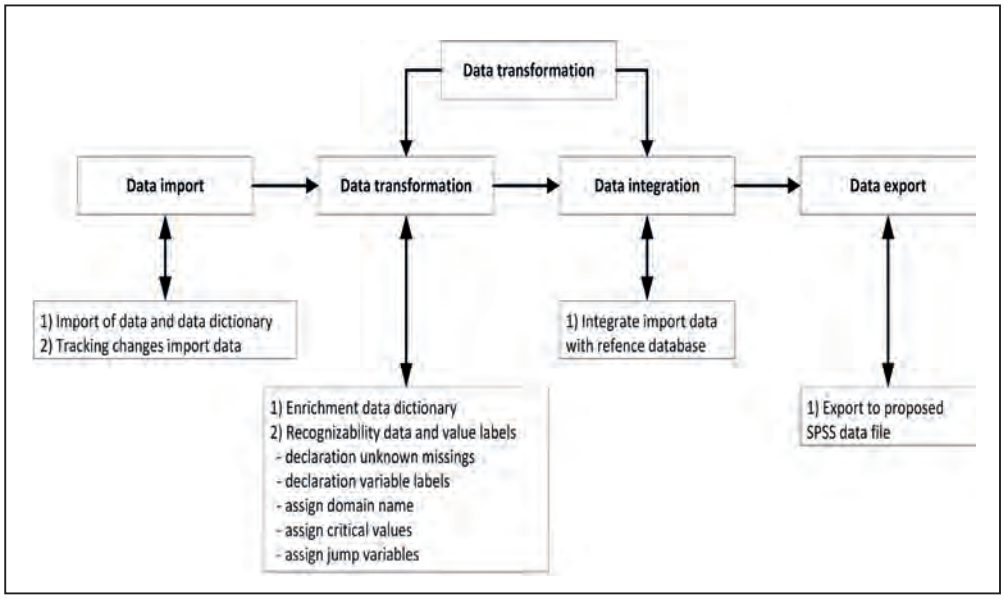
We will examine the original data for completeness and consistency using the following protocol: summary statistics for all variables will be sent back to collaborators to verify categories, units of measurements, and comparing baseline characteristics with previous publications. In addition, we will verify consistency of data within individuals, highlight potential outliers and identify missing data. Any data queries will be discussed and resolved directly with the responsible collaborating principal investigator.

Harmonization

To harmonize variables, we will collect information from all studies and follow a conversion procedure consisting of four steps: 1) importation of data into the data warehouse; 2) preparation for transformation of original studies, including variable

checking; 3) transformation of the data labels of the original studies into the POLARIS coding scheme and integration into the data warehouse; and 4) export of specific variables into a SPSS data file for the proposed statistical analyses. POLARIS data management processes from the original data sets from collaborating principal investigators to the formation of the POLARIS database is described in more detail in Figure 4.2.

Figure 4.2. Data harmonization process



Data confidentiality

Data made available for the POLARIS database will remain the property of the investigators supplying the data. Any data supplied will be held securely at the EMGO Institute for Health and Care Research and will be treated as confidential. All data included in the POLARIS project will be anonymized by the principal investigators prior to data transfer to the POLARIS center (if this has not already been done). Only RCTs that had ethical committee approval will be included in the POLARIS database.

Statistical analysis

We will conduct one-stage IPD meta-analyses to evaluate the effect of physical activity, exercise and psychosocial interventions on HRQoL compared with wait-list, usual care or attention control group. This will involve multilevel regression analyses with a two-level hierarchical structure: the patients within each trial as level 1 and the trial as level 2.

Moderators

To conduct the statistical analyses, we will pool individual patient data from RCTs contained in the POLARIS database. To test for moderating effects, we will use moderated multiple regression analyses (MMR) [32]. MMR is an extension of a multiple regression equation that includes an interaction term providing information regarding a potential moderating effect. The selection of moderators will be based on a specific rationale – theory or evidence based – model of why the intervention may be more effective for some subgroups than for others. We will examine interactions between the intervention and potential categorical moderators (i.e., demographic, clinical and personal factors plus treatment such as age, marital status, disease stage, type of treatment (e.g., chemotherapy) and baseline functioning). The regression coefficient of the interaction term provides information on whether the effect of the intervention on the outcome differs across different moderator categories. Before conducting MMR, we will check the homogeneity of (within-group) error variance, i.e., whether the error variance for one moderator group is equal to the error variance in the other moderator group(s) [32]. We will do this by examining whether the residual variance is constant across the moderator categories.

Predictors

We will conduct multivariable backward logistic regression analyses on pooled data to develop prediction models [33, 34]. We will explore the need to account for trial variability in these models. The variables with the highest p-values will be removed one by one, based on the Wald test, until all remaining variables have a significant

pre-determined p-value. Potential predictors include sociodemographic, clinical and personal and treatment characteristics at baseline. Relevant moderators identified will also be taken into account when building the prediction model. Subsequently, the predictors included in the model will be checked for interactions with treatment by introducing interaction terms into the model, and evaluating their contribution to the model. We will calculate the probabilities of success for the different categories of the predictors interacting with treatment [35]. We will evaluate the performance of the regression model using the Hosmer-Lemeshow goodness-of-fit test, and the discriminative ability of the regression model using the area under the receiver operating characteristics (ROC) curve and its 95% confidence interval. Internal validation of the model will be determined by a bootstrapping procedure with 200 replications. In each replication, a random sample from the original dataset is drawn with replacement. We will multiply the regression coefficients by the shrinkage factor derived from the bootstrapping procedures to quantify the amount of optimism and to correct for over-fitting if necessary.

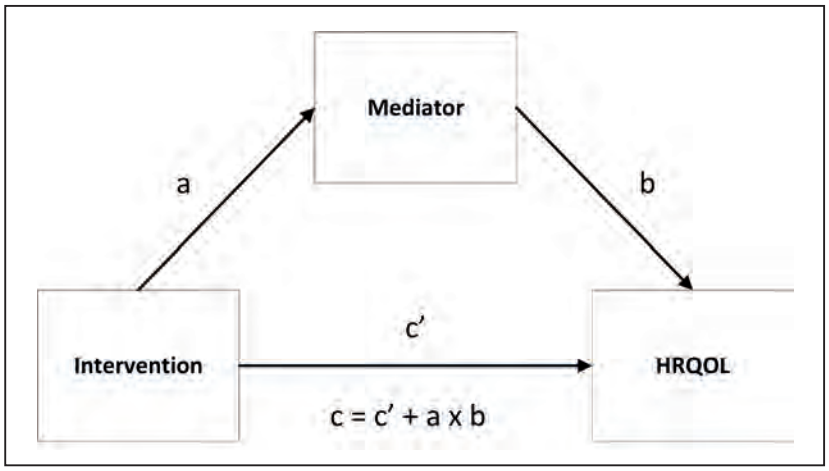
Finally, we will try to translate the clinical prediction model into a clinical decision rule that may assist patients and clinicians in making the most objective, evidence-based and well-considered choice for optimal physical activity, exercise or psychosocial interventions to improve HRQoL. This model may guide treatment choice and may predict which patient will benefit most from a specific treatment.

Mediators

Potential mediators of the intervention effect on HRQoL will be explored according to the product-of-coefficients test described by MacKinnon (Figure 4.3) [36]. The selection of mediators will be based on the theoretical framework of the included studies. First, we will estimate the total intervention effect on the outcome (path c). Second, we will estimate the intervention effect of the hypothesized mediator (path a). Third, we will estimate the association between the mediator and outcome, adjusted for the intervention effect (path b). The final regression model provides estimates for the b-value and for the direct association (c'-path). The product of coefficients (a × b) provides an estimate of the relative strength of the mediation effect. The proportion mediated will be estimated by dividing the mediation effect (a×b) by the total direct effect (c= c'+ a×b). Subsequently, a bootstrapping method

(with n=5000 bootstrap resamples) will be used to calculate the bias corrected confidence intervals around the mediated and direct effects using the SPSS macro suggested by Preacher and Hayes [37]. In case of multiple mediators, path models and structural equation models will be constructed [36].

Figure 4.3. Mediation analysis



HRQOL= health related quality of life

Project management

A Steering Committee (i.e. LMB, JK, IMVdL, JB) has been established and is responsible for the coordination of the POLARIS project, advised by an international advisory board consisting of experts in this research field (i.e. NKA, KSC, PBJ, RUN). Project coordination and statistical analyses will be conducted at the EMGO Institute for Health and Care Research and the Department of Epidemiology and Biostatistics of VU University Medical Center, Amsterdam. Collaborating investigators are welcome to propose additional research projects, to develop analysis protocols and to spend time at the coordinating center conducting data analysis. The steering committee will check for potential overlap with other proposals, and subsequently, all collaborators will be contacted to ask permission for the use of their data for the proposed analysis. Collaborators may decline participation on a study-by-study basis, and have the right to withdraw their data for future analyses.

Publication policy

The results of the specific meta-analyses will be presented to and discussed with all collaborators during a collaborators meeting. Subsequently, the results will be published in scientific peer-reviewed journals. The primary publications will be in the name of the writing committee as well as the collaborative group. The writing committee for these primary publications will consist of the research staff working in the analysis center and those collaborators who have expressed interest in that particular analysis. All co-authors need to comply with the criteria of the Vancouver Protocol for co-authorship. The POLARIS consortium will be listed as a group author, and all participating studies and investigators contributing to this project will be listed at the end of each publication.

Discussion

The POLARIS consortium will conduct the first IPD meta-analyses based on individual patient data, with the goal of more effectively targeting physical activity, exercise or psychosocial programs to cancer survivors. Furthermore, insight into the moderators explaining which physical activity, exercise or psychosocial intervention can improve HRQoL for whom and under what circumstances is an essential step towards personalized care for cancer survivors. IPD meta-analysis allows for testing of interactions to evaluate whether patient and setting characteristics are statistically significantly related to treatment effects. Further, it may allow us to build a clinical decision rule supporting evidence-based decision making about which intervention would be most effective for a given outcome and a given patient group. This can be an essential step to improve care and optimize the patient's HRQoL in an efficient and evidence-based way. It may also help to identify subgroups of patients for which effective interventions are not yet available and thus need to be developed and evaluated.

Despite the strong study design allowing sophisticated statistical analyses, an IPD meta-analysis is at risk for 'retrieval bias' if not all investigators of relevant studies are willing or able to participate. However, estimated effect sizes may still be valid because it is unlikely that non-participation is associated with effect size.

In summary, the POLARIS consortium will start to carry out a series of

IPD meta-analyses evaluating the effectiveness of physical activity, exercise and psychosocial interventions on the HRQoL of cancer survivors in order to identify relevant moderators of intervention effects, and will try to build a clinical prediction rule that may support evidence-based decision making about which interventions are most likely to be effective at the individual patient level.

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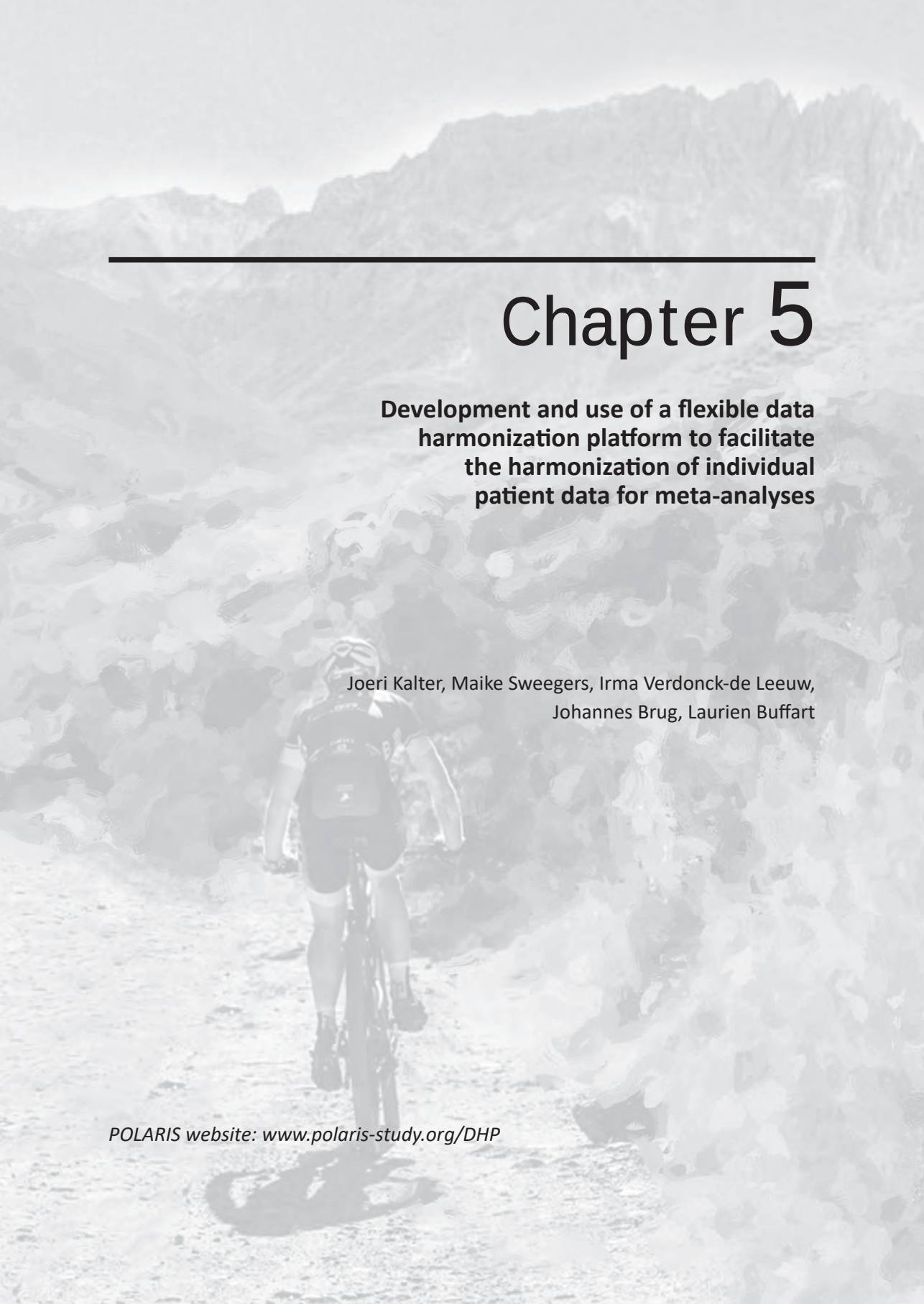


Chapter 5

Development and use of a flexible data harmonization platform to facilitate the harmonization of individual patient data for meta-analyses

Joeri Kalter, Maike Sweegers, Irma Verdonck-de Leeuw,
Johannes Brug, Laurien Buffart

POLARIS website: www.polaris-study.org/DHP

Abstract

Objective: Harmonizing individual patient data (IPD) for meta-analysis has clinical and statistical advantages. Gathering and harmonizing IPD from multiple studies may benefit from a flexible data harmonization platform (DHP) that allows harmonization during data collection. This paper describes the development and use of a flexible DHP that was initially developed for the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study.

Materials and Methods: We developed a DHP that (I) allows IPD harmonization with a flexible approach, (II) has the ability to store data in a centralized and secured database server with large capacity, (III) is transparent and easy in use, and (IV) has the ability to export harmonized IPD and corresponding data dictionary to a statistical program.

Results: The DHP uses Microsoft Access as front-end application and with a relational database management system such as Microsoft Structured Query Language (SQL) Server or MySQL as back-end application. The DHP consists of five user interfaces which support the user to import original study data, to harmonize the data with a master data dictionary, and to export the harmonized data into a statistical software program of choice for further analyses.

Discussion and Conclusion: The DHP uses a flexible strategy to harmonize multiple datasets during data collection. It is transparent, easy to use, and time efficient, especially when IPD of a large number of studies need to be harmonized. The DHP is currently being used in the POLARIS study and in two other IPD meta-analyses.

Background

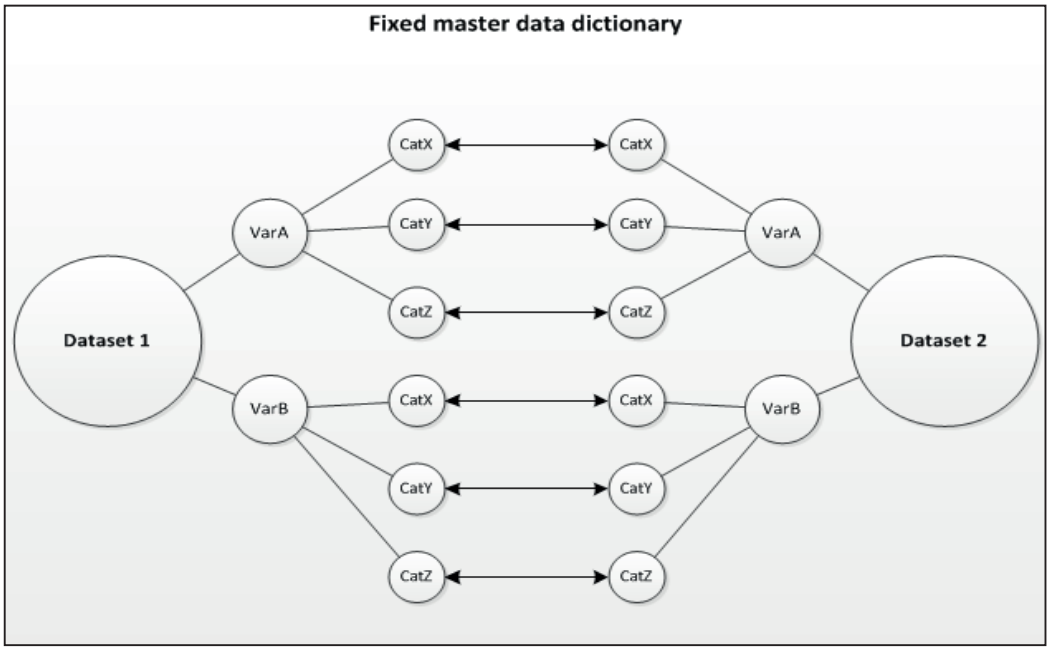
Meta-analyses that synthesize results of multiple studies inform health professionals about the best available care and are an essential part of evidence-based medicine [1, 2]. A meta-analysis on individual patient data (IPD) is regarded as the gold standard for meta-analysis [3] because it allows standardized analytical techniques across studies, the testing of interaction effects with covariates at the level of the patient, and the use of consistent analyses for time-to-event outcomes [4, 5].

Gathering and harmonizing IPD from individual studies is dependent on response of principal investigators (PI's) from the original study, their time to prepare their data for data sharing, or on privacy, ethical or legal issues [6]. Additionally, researchers conducting the IPD meta-analysis may face difficulties with harmonizing IPD because different studies often used different coding schemes or constructs [7].

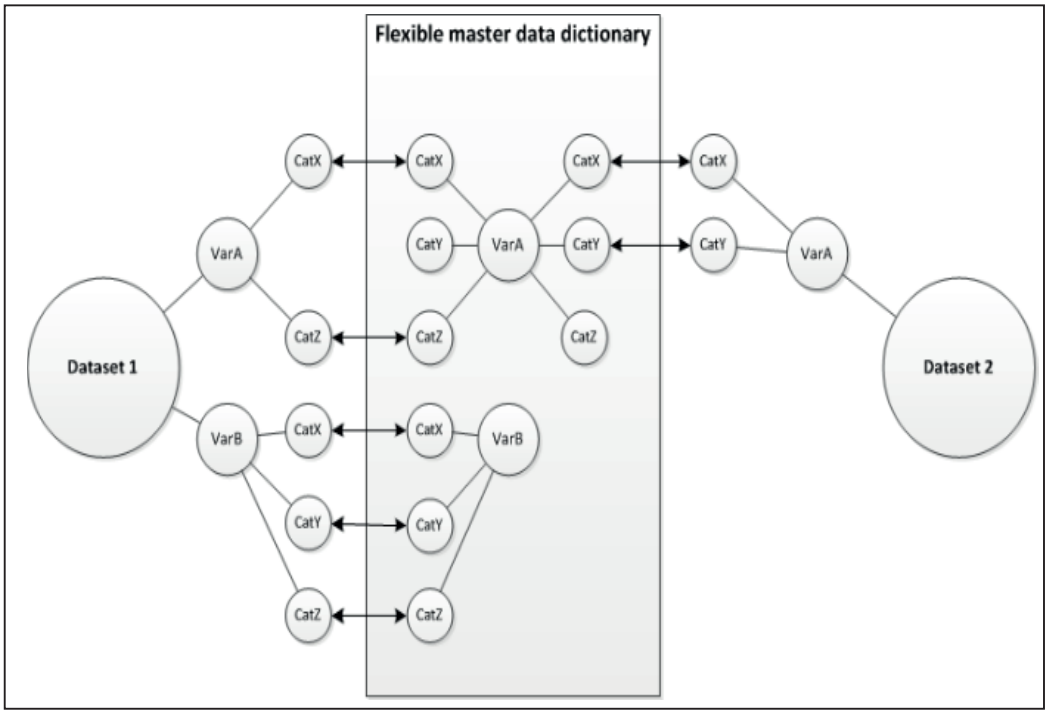
Different strategies can be used to harmonize IPD from multiple studies. Data can be transformed from the original data dictionary (i.e. a codebook with descriptions of variable names and value labels, variable type, format, and missing values) [8] to a fixed master data dictionary that defines similar and overlapping data from all studies (Figure 5.1a). This fixed master data dictionary can be defined prospectively (before data collection) or retrospectively (after all data has been retrieved), each with their specific challenges. A prospectively defined master data dictionary is time consuming when certain variables are defined differently across studies. For example, if age was assessed as a continuous variable in most studies (e.g. age in years), but as a categorical variable (e.g. <50 vs. ≥50 years) in a newly retrieved study, all previously retrieved study data need to be transformed into categorical data in order to harmonize the datasets. On the other hand, retrospectively defining a master data dictionary can only be done after data collection of all variables of interest of identified studies has been completed. However, when the number of variables and datasets is large, it is more time-efficient to start harmonizing the data as soon as IPD from the first studies have been received. This way, data analyses can start soon after data collection has been completed. This requires a flexible strategy to harmonize IPD, allowing adaptations when new studies and/or variables with different coding schemes are included (Figure 5.1b) is probably the best option.

We built a flexible data harmonization platform (DHP) to harmonize IPD from multiple studies. The DHP was primarily built for the Predicting OptimaL cAncer

Figure 5.1. Harmonization model with a fixed (5.1a) and flexible (5.1b) master data dictionary



5.1a. In a harmonization model with a fixed master data dictionary, single study's data dictionary are adjusted and harmonized (arrow lines) to a master data dictionary that defines similar data from all studies



5.1b. In a harmonization model with a flexible master data dictionary, the original study variables are harmonized on each category (arrow lines) with a master data dictionary that can be adapted

RehabIlitation and Supportive care (POLARIS) study [9-11], in which we harmonized IPD from – so far – 57 randomized controlled trials to conduct an IPD-meta-analysis to evaluate the effects of physical activity or psychosocial interventions on health-related quality of life in patients with cancer, and to identify moderators of the intervention effects [9]. The DHP has currently been implemented in two studies [12, 13]. In this paper, we describe the development and use of the flexible DHP to facilitate harmonization of IPD for meta-analyses.

Materials and methods

We developed a DHP that had to meet the following requirements: (I) allowing IPD harmonization with a flexible approach, (II) having the ability to store data in a centralized and secured database server with large capacity, (III) being transparent and easy in use, and (IV) having the ability to export harmonized IPD and corresponding data dictionary to statistical programs such as SPSS [14], SAS [15], or STATA [16].

Infrastructure DHP

To develop such a DHP, we used Microsoft Access as front-end application. The front-end application includes interfaces that directly communicate with users and forward requests to a back-end server to retrieve requested data or perform a requested service. The back-end server that can be used for this application is a relational database management system, such as Microsoft Structured Query Language (SQL) Server or MySQL.

Microsoft Access was used for its ability to link with data files of different statistical software packages – including SPSS, SAS, and STATA – and to transfer both the data and the corresponding data dictionary, into multiple tables in the relational database management system. The front-end application is linked to the tables in the relational database management system using an open database connectivity that enables communication between the front-end application and the relational database management system. To improve performance of the front-end application, we created pass-through queries that run statements that select,

insert, update, and delete information in the relational database management system.

Software requirements

To function adequately, the DHP has specific software requirements. The following software must be installed: Microsoft Access 2010 (or newer), and a relational database management system such as Microsoft SQL Server or MySQL. Furthermore, Microsoft Access uses multiple required references that enable the DHP to communicate with statistical software programs. The Microsoft Access references required for adequate function of the DHP are: Visual Basic For Applications, Microsoft Access 14.0 object library (or newer), Microsoft Visual Basic for Applications Extensibility 5.3, OLE Automation, System_Windows_Forms, Microsoft ActiveX Data Objects 2.5 Library, Microsoft Scripting Runtime, mscorlib.dll, System, Microsoft Office 14.0 Access database engine Object Library (or newer), and Microsoft Windows Common Controls 6.0 (SP6).

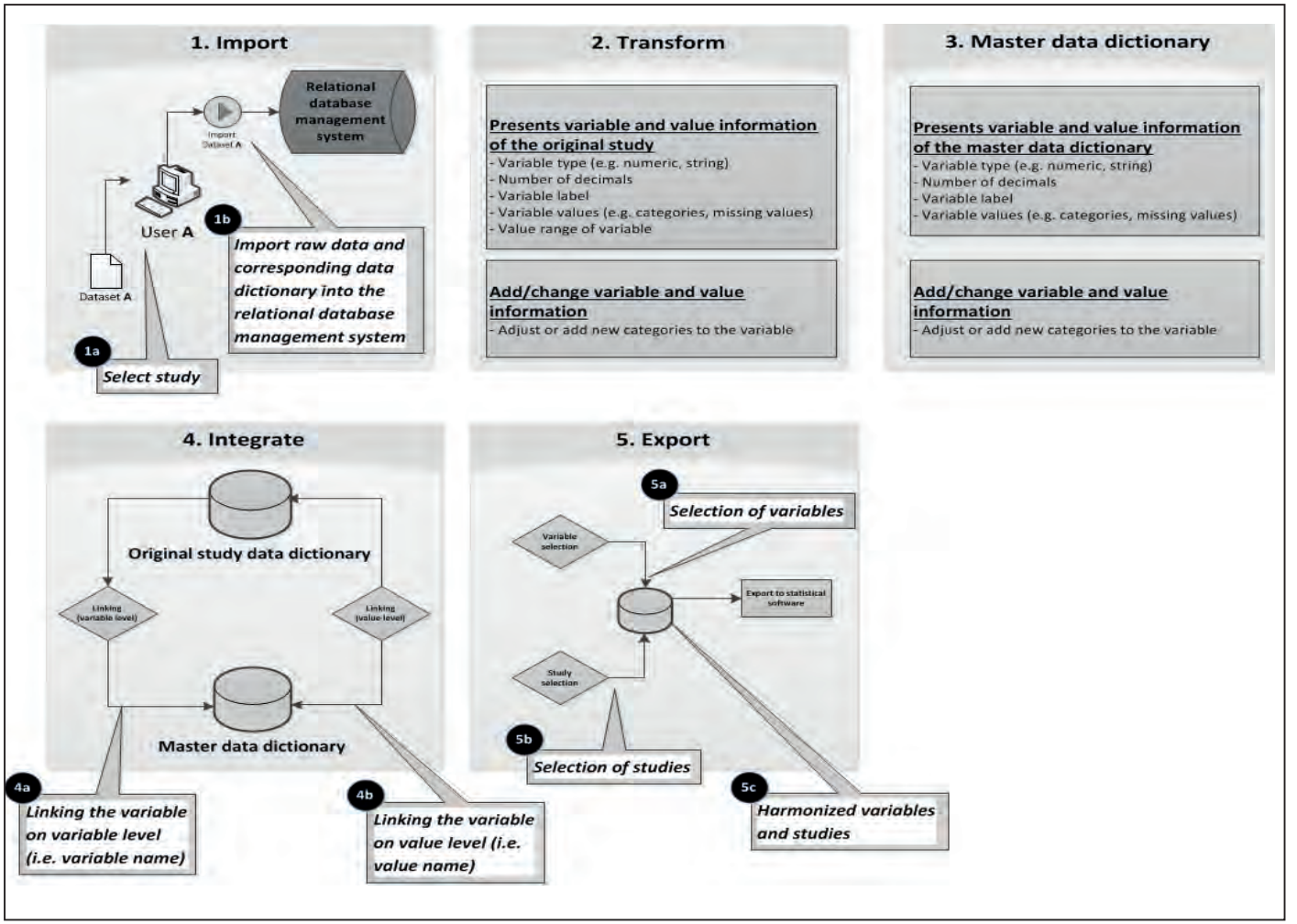
User interfaces of the data harmonization platform

The front-end application consists of 5 user interfaces, each with a separate function: (I) an import interface; (II) a transform interface; (III) a master data dictionary interface; (IV) an integration interface; and (V) an export interface (Figure 5.2). These interfaces support the user with importing and harmonizing the original study's data dictionary with the master data dictionary, and exporting the raw data of all selected variables and studies of interest into one harmonized dataset. A further explanation of the user interfaces is provided below.

I. *Import*

The import interface enables the user to select and import raw data and corresponding data dictionaries from original studies.

Figure 5.2. User interfaces of the data harmonization platform



II. *Transform*

The transform interface shows the data dictionary from the original study, and presents the type (e.g. numeric, string), number of decimals, label, values (i.e. categories and missing values), and value ranges (i.e. minimum and maximum value) of each variable. Accurately defining and labeling categories and missing values are essential to link the original study data dictionary with the master data dictionary [7]. Therefore, the transform interface enables users to make adjustments or to add new categories to the variables when necessary. For instance, if missing values are not defined as such, these values cannot be linked with the master data dictionary. Consequently, the data would incorrectly be imported as new numeric data into the harmonized dataset and not as missing data. This would affect the outcome of the analyses in an incorrect manner, and therefore this transform interface is crucial to accurately harmonize the IPD into the new dataset.

III. *Master data dictionary*

The master dictionary interface shows the master data dictionary, and enables the user to add or adjust variables and/or categories in the master data dictionary during the data collection of eligible studies. It further gives information about the types, labels, number of decimals, and values of the variables in the master data dictionary and enables the user to make adjustments to this information.

IV. *Integration*

The integration interface enables the user to link the variable from the original study with the master data dictionary. The linking of variables occurs on the level of the variable itself (i.e. variable names) and on the value level (i.e. value definitions). It further presents which variables from the original study are linked to the master data dictionary and which are not. Finally, it has the flexibility to disconnect linked specifications at the variable and/or value level, when a link was incorrect.

V. *Export*

The export interface enables the user to create a harmonized dataset from selected variables and from studies of interest in a preferred statistical software program.

Results

In this section, we describe how to use the different interfaces of the DHP that support data harmonization. For these descriptions, we use examples from the POLARIS study as proof of concept for which the DHP was initially developed.[10] Currently, the database of POLARIS includes IPD from almost 10,000 patients from 57 randomized controlled trials [9-11].

POLARIS-specific software components

For POLARIS, the front-end application is connected with Microsoft SQL Server 12.0. This server has been set up at the VU University Medical Center, Amsterdam, The Netherlands. The DHP is secured by user identifier and password, and accessible for POLARIS consortium members that are authorized by the POLARIS steering committee. In addition, the DHP has been set up to import SPSS data files, as most data files in POLARIS were provided in SPSS format. This requires SPSS to be installed, as well as the following references in Microsoft Access: SPSS Statistics Type Library, and SPSS Statistics Legacy Type Library.

Function of the DHP user interfaces

I. *Import*

In the import interface, the user selects the dataset from the original study and starts the import process by pressing the import button. The import of data is a fully automatic process that includes the following five steps:

In the first step, the DHP imports the raw data into a newly defined table in the relational database management system. In the second step, the DHP stores the

data dictionary from the original study in three empty temporary data dictionary tables: one including study information (e.g. study name, source file pathname, import date of the study, and person responsible for the import of the study), one including variable information (e.g. variable name, type, labels, missing values, and study identifier), and one including value information (e.g. value definitions of categories and missing values (system and user) of specified variables, and study identifier). In the third step, the DHP compares the study, variable names, and value definitions of the imported study stored in the temporary data dictionary tables, with those stored in three identical structured permanent data dictionary tables. Comparing the temporary data dictionary tables with the permanent tables is a fully automatic process that distinguishes four differences: I) The original study that is included in the temporary data dictionary table has no corresponding study identifier in the permanent data dictionary table; II) the variable names and/or value definitions in the temporary data dictionary table(s) have no corresponding variable names and/or value definitions in the permanent data dictionary table(s); III) the variable and/or information included in the temporary data dictionary table(s) (e.g. type of variable) does not correspond with the variable and/or value information in the permanent data dictionary table(s); and IV) the variable names and/or value definitions that are included in the permanent data dictionary table(s) have no corresponding variable names and/or value definitions in the temporary data dictionary table(s) (Table 5.1).

In the fourth step, the DHP imports the raw data from the original study into an entity-attribute-value table. This table consists of unique rows where each attribute-value pair describes one attribute of a given entity. The entity represents a subject identifier of an original study, for example '232' in case the subject identifier from the original study is 232. The attribute represents an entity, for example the variable 'Age'. The value is the value of that attribute, for example '59' in case the age is 59 years.

In the final step, the DHP produces a table containing the 5 highest and the 5 lowest values, including system missing values, of all variables to inform the user in the transform interface about the value range of each variable.

Table 5.1. The four differences between the temporary and permanent data dictionary tables that may occur in study and variable names, and value definitions, and the response of the DHP to this difference

Number	Identified difference between the temporary and permanent data dictionary tables	DHP response
I	The original study that is included in the temporary data dictionary table has no corresponding study identifier in the permanent data dictionary table.	The DHP recognizes this as a new study, and adds the original study with associated variable names and value definitions and corresponding variable names and value definitions (e.g. types, number of decimals, labels, categories, and missing values) to the permanent data dictionary tables.
II	The original study has previously been included in the DHP (i.e. information about the original study is in the permanent data dictionary table), but the variable names and/or value definitions included in the temporary data dictionary table(s) have no corresponding variable names and/or value definitions in the permanent data dictionary table(s).	The DHP identifies this as a new variable name and/ or value definitions in the original study, and adds the variable name and/or value definitions along with the corresponding variable names and/or value definitions to the permanent data dictionary table(s).
III	The original study has previously been included in the DHP, and although the variables names and/or value definitions in the temporary data dictionary table(s) match those in the permanent data dictionary table(s), the variable and/or value information in the temporary data dictionary table(s) does not correspond with the variable and/or value information in the permanent data dictionary table(s).	The DHP will update the variable type from string to numeric in the permanent data dictionary, when, for example, the type of the variable in the temporary data dictionary has a numeric format, but the type of variable in the permanent data dictionary has a string format.
IV	The original study has previously been included in the DHP, but the variable names and/or value definitions that are included in the permanent data dictionary table(s) have no corresponding variable names and/or value definitions in the temporary data dictionary table(s).	The DHP recognizes this as a deleted variable name and/or value definition from the original study, and inactivates the variable name and/or value definition in the permanent data dictionary table(s). Consequently, the user cannot harmonize these variables and/or values.

II. *Transform*

In the transform interface, the user manually selects a variable name from the original study that he or she wants to check and prepare for linking with the master data dictionary. First, the user checks if the label clearly describes the corresponding variable (e.g. patient's age in years at baseline, Figure 5.3). Defining the label is essential for linking the correct variable name with the corresponding variable name in the master data dictionary. Next, the user checks if the variable is a continuous or a categorical variable. Categories and missing values need to be linked as categories with the master data dictionary and should therefore be described. If categories and missing values are not described, the user can add the value definition identifying the category and missing value by using the "add value to variable" button (Figure 5.3).

Figure 5.3. Screenshots from the transform interface where the data dictionary of the original study is presented (in the 'Current Value' grey fields). It presents the user (1) the variable type (e.g. numeric), number of decimals (e.g. '0'), and label (e.g. 'Age'), (2) values (i.e. categories, and user ('9999') and system missing ('SYSMIS') values) of the variable, and (3) value ranges (i.e. five highest and five lowest values) of the variable. It further enables the user to make adjustments to the variable and value information and to add new categories to the variables when necessary (in the 'New Value' white fields)

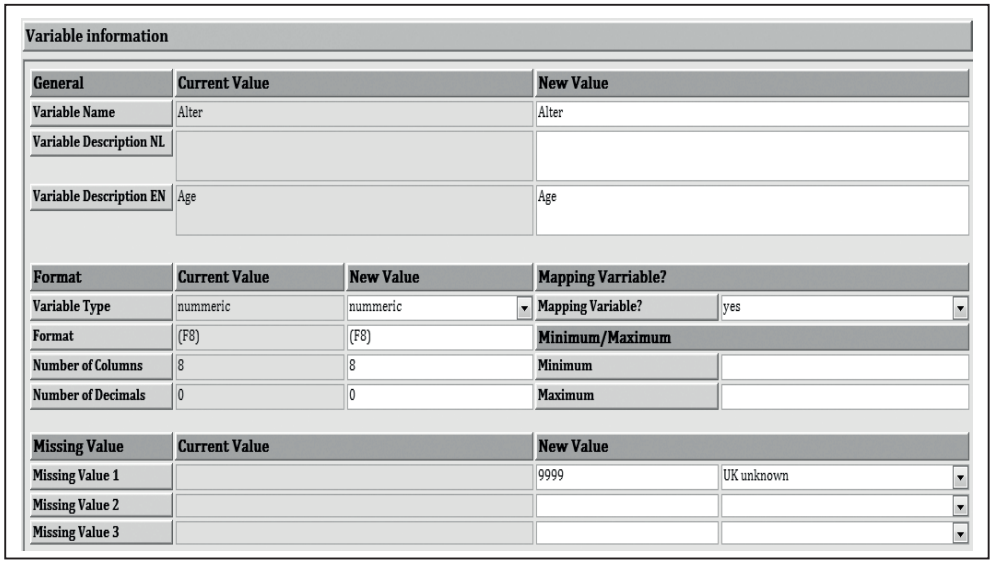
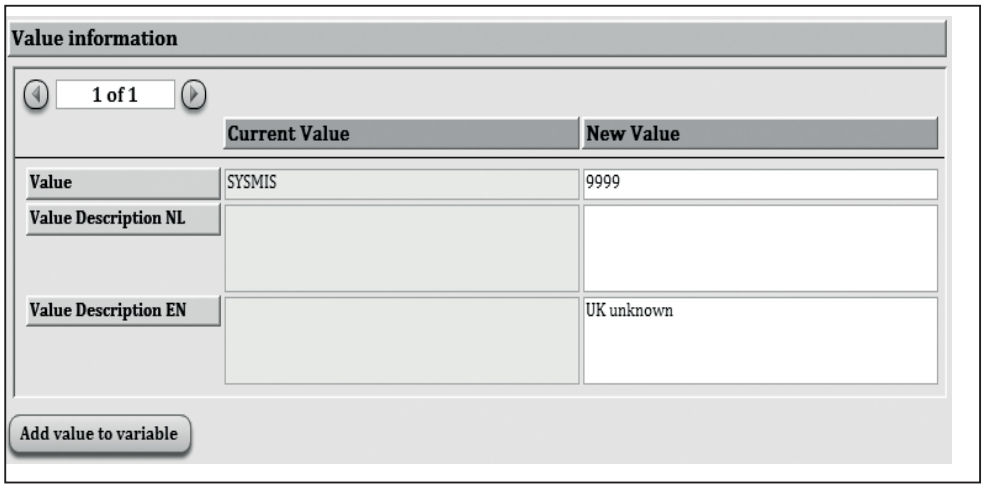


Figure 5.3 (continued)



Top 5 highest and lowest values

Top 5 highest values	Variable	Top 5 lowest values	Variable
70	Alter	18	Alter
68	Alter	20	Alter
67	Alter	21	Alter
66	Alter	22	Alter
65	Alter	23	Alter

III. *Master data dictionary*

In the master data dictionary interface, the user has insight in all variable names and value definitions with the corresponding information described in the master data dictionary, including, among others, the type (e.g. continuous, string, or categorical), the number of decimals, and values (i.e. categories and missing values) of the variable. It does, however, not present which variable names and/or value definitions have been linked with the corresponding variable names and/or value definitions from the original studies.

IV. *Integration*

In the integration interface, the user selects variables from the original study that

need to be linked with the master data dictionary. For example, in the POLARIS study, we linked the variables 'Alter' (German for 'age') and 'Geschl' (abbreviation for geschlacht, which is German for sex) from a German study with the master data dictionary (Figure 5.4). The variable 'Alter' is a continuous variable representing the age of a patient at baseline. The variable 'Geschl' is a categorical variable that represents the sex of a patient, with the value '1' representing male and '2' representing female.

In order to harmonize these variables with the master data dictionary, the user performs several steps:

First, the user selects the variable 'Alter' or 'Geschl' from the original study to be harmonized. Subsequently, the interface automatically shows the corresponding value definitions in a value list. As value definitions from continuous variables do not differ between studies (i.e. the value '59' for a patient's age is similar across studies), only value definitions from categorical and missing values need to be linked with the master data dictionary. Consequently, when selecting the variable 'Alter', the interface only shows the codes and labels for missing values (i.e. the value code '9999' with a corresponding label 'Unknown', Figure 5.4). When selecting the variable 'Geschl', the interface shows the missing values, and categories with the corresponding labels (i.e. the value definitions '1' and '2' with the corresponding labels 'male' and 'female', respectively).

Second, the user selects a variable name to be harmonized from the master data dictionary that corresponds with the selected variable from the original study. For example, the variable 'Alter' is described in the master data dictionary as 'Age' with the label 'Age (years)'. After selecting the variable 'Age' from the master data dictionary, the integrate interface automatically shows the corresponding values with labels from this variable (i.e. the value '9999' with label 'Unknown / do not know'). In case the variable 'Age' and/or the missing value definitions are not described in the master data dictionary, the user opens the master data dictionary interface and adds the variable 'Age' in the master data dictionary using the "add variable" button. Next, the user describes the variable information of 'Age' (e.g. continuous variable), and adds the missing value definition '9999' with label 'Unknown' to define the missing value by using the "add value" button.

Third, the user links the variable 'Age' with the variable 'Alter' on two levels;

on variable name (i.e. 'Alter' is linked with 'Age' from the master data dictionary), and on value definition (i.e. the missing value '9999' with label 'Unknown' from 'Alter' is linked with the missing value '9999' with label 'Unknown / do not know' from 'Age', Figure 5.4). The variable 'Geschl' from the original study is linked with 'Sex' from the master data dictionary. On value level, the definitions '1' with label 'male', '2' with label 'female', and '9999' with label 'Unknown' from the variable 'Alter' are linked with '0' with label 'male', and '1' with label 'female', and '9999' with label 'Unknown / do not know' from 'Sex', respectively.

V. *Export*

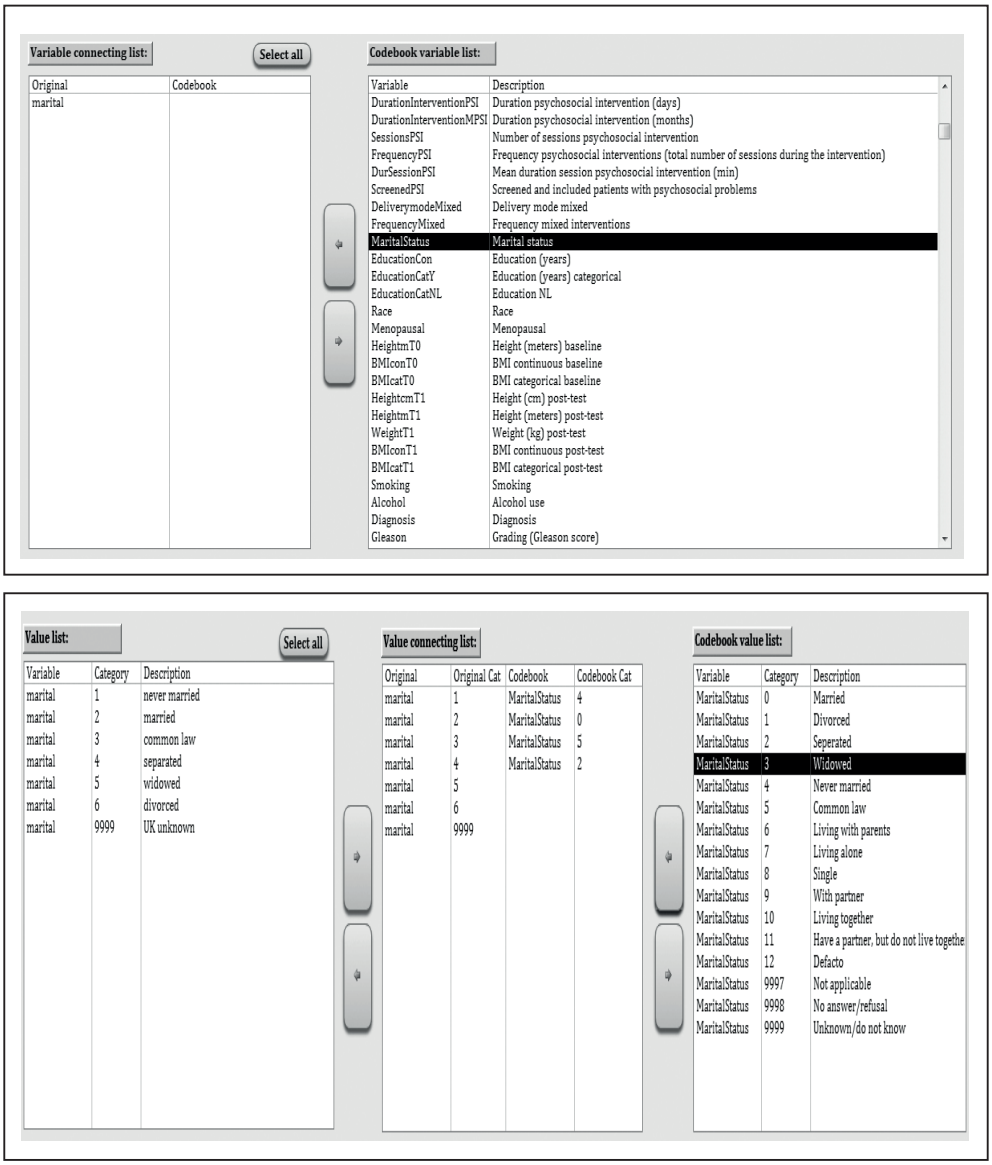
In the export interface, the user creates a harmonized dataset in a preferred format to be able to proceed with the proposed statistical analyses. For POLARIS, we created harmonized datasets in SPSS. The export process includes the following steps:

First, the user selects variable names to be harmonized from the variables presented in the master data dictionary. For example, the user selects the variable names 'Age' and 'Sex'. Second, the user selects the studies to be harmonized from all the imported studies that are presented in the master data dictionary study identifier. For example, the user selects the three imported studies with study identifier '6', '8', and '15'. Third, the user starts the fully automatic export process by pressing the 'create file' button. In this process, the DHP combines all raw data from the selected variables and studies – with the corresponding data dictionary as described in the master data dictionary – into a newly defined table in the relational database management system (i.e. presented as 'tblExport', Table 5.2).

This table has a long format, where each row in this example represents a variable name (e.g. 'Age') and value definition (e.g. '59') of a newly created subject identifier from the original study (e.g. '600232' has been created from the original subject identifier '232' and the subject's related study identifier '6', Table 5.3).

Each row also provides information on the subject's related study identifier (e.g. '6'), the rank of the variable (i.e. the ranking order of the variable name column in the exported dataset), and the country identifier (e.g. the country identifier '1' represents 'The Netherlands'). Next, the DHP runs an algorithm that creates a

Figure 5.4. Screenshots from the integrate interface that enables the user to link the variable of the original study with the master data dictionary. The linking of variables occurs on (1) the level of the variable itself (i.e. variable names) and (2) on the value level (i.e. value codes). It has further the flexibility to disconnect linked specifications at the variable and/or value level using the arrow buttons, when, for example, a link was incorrect



syntax in a statistical software program (e.g. SPSS). In this syntax, the DHP copies a number of commands that creates a dataset from the raw data of the 'tblExport' into the statistical software program (Table 5.4).

Table 5.2. Example of the table 'tblExport' where all the raw data of the selected variables and studies with the corresponding variable name ('VarCode') and value definition ('ValDef') as described in the master data dictionary

SubjId	StudyId	CountryId	VarCode	ValDef
600232	6	1	Age	59
600232	6	1	Sex	1
800056	8	7	Age	67
800056	8	7	Sex	0
150101	15	10	Age	54
150101	15	10	Sex	1
…	…	…	…	…

Abbreviations: SubjId= subject identifier; StudyId= study identifier; CountryId= country identifier

Table 5.3. Example of a restructured dataset in SPSS that has been reshaped from a long data file (see Table 5.2) into a wide data file

SubjId	StudyId	CountryId	Age	Sex
600232	6	1	59	1
800056	8	7	67	0
150101	15	10	54	0
…	…	…	…	…

Abbreviations: SubjId= subject identifier; StudyId= study identifier; CountryId= country identifier

These commands include: I) a command to import the data stored in the 'tblExport' into the statistical software program, II) a command to restructure the imported data from a long format into a wide format, III) a command to set variables that are not included for some studies into study missing, IV) a command to set the data dictionary for each corresponding variable in the newly created dataset, and

V) a command that saves the data file into a specified folder. For POLARIS, we also added a command to filter the SPSS dataset on specific patient characteristics, so that the dataset can, for example, be filtered on patients with breast cancer by selecting breast cancer from a list of cancer types on the export interface.

Running the complete syntax creates a harmonized SPSS dataset including all selected variable names and studies that enables further analysis.

Table 5.4. The five commands that creates a dataset from the raw data of the 'tblExport' into the statistical software program

Syntax command	Explanation
Importing data stored in the 'tblExport' into the statistical software program	For POLARIS, SPSS retrieves the data from the 'tblExport' using the 'get data' command. With this command, SPSS selects the data stored in the 'tblExport' via an open database connectivity and import the data into a new defined SPSS dataset.
Restructuring imported data from a long format into a wide format.	In SPSS, the data are restructured by the 'casestovars' command. With this command, the data stored in the 'tblExport' are reshaped, making one row per subject identifier that would contain the subject's related study identifier, the country identifier, 'Age', and 'Sex' as variables (Table 5.3).
Setting variables that are not included for some studies into study missing.	For example, if the variable 'Age' is not included in a study, all values of 'Age' within this study is set to the missing value '9997' with label 'Study missing'.
Setting the data dictionary for each corresponding variable in the newly created dataset.	For example, the variable 'Age' is set to a continuous variable, with two decimals, and has '9997' with label 'Study missing', '9998' with label 'not applicable (N/A)', and '9999' with label 'Case missing' as missing values. The variable 'Sex' is set to a categorical variable, has '0' with label 'male' and '1' with label 'female' as categories, and has '9997' with label 'Study missing', '9998' with label 'N/A', and '9999' with label 'Case missing' as missing values.
Saving the data file into a specified folder.	For POLARIS, the data files are stored on a secured server that is only accessible for authorized POLARIS consortium members.

POLARIS= Predicting OptimaL cAncer RehabIlitation and Supportive care, SPSS= Statistical Package for the Social Sciences

Discussion

This paper describes the development and use of a flexible DHP that I) facilitates harmonization of IPD already during the process of collecting data from multiple studies, II) allows to store, prepare, and harmonize IPD within one transparent platform, III) is easy in use, and IV) has the ability to export harmonized IPD and corresponding data dictionary to a statistical program for further analysis.

To the best of our knowledge, this is the first paper that describes a DHP that allows starting data harmonization already during data collection, which is time efficient, especially when the number of studies is large. With the increasing use of IPD meta-analysis [4], our flexible DHP helps managing the time necessary to harmonize IPD.

In contrast to previous DHPs that use a centralized platform providing access to remote datasets that are stored and managed separately by each PI of the original studies [7, 17], our DPH has the ability to store, prepare and harmonize IPD within one transparent DHP. In these previous DHPs, all PI's of original studies needed to transform their datasets to a defined master data dictionary before harmonization could take place. In contrast, by using one centralized platform for data transformation, the time burden for the PI of the original study is reduced. Our DHP is user-friendly, requiring minimal technical knowledge from the user. Instead of using syntaxes in statistical software [18], the harmonization process is facilitated by transparent interfaces, easy in use.

Our DHP enables exporting harmonized IPD and corresponding data dictionary to a statistical program of choice, creating more flexibility than offered in previous DHP [18].

To guarantee security of data, the DHP requires storage of the original datasets at one single secured location. To make explicit how and when the data is used, we have developed data sharing agreements for data access, use, and intellectual property arrangements [9]. Additionally, only fully anonymous datasets are shared by the PI's of the original studies to ensure privacy of study participants [19].

The DHP is currently limited to import and export data files that are in SPSS format only. To be implemented in IPD meta-analyses that prefer other statistical

analyses software formats, such as SAS or STATA, additional algorithms must be written.

Our DHP has successfully been used for the POLARIS study [10, 11], and other international consortia [12] [13]. The flexible DHP described in this paper facilitates harmonization of IPD already during the process of collecting data from multiple studies, allows to store, prepare, and harmonize IPD within one transparent platform, is easy in use, and has the ability to export harmonized IPD and corresponding data dictionary to a statistical program for further analysis. The DHP is currently being used in enriching the POLARIS study with data of new RCTs now and in the future, and in two other IPD meta-analyses. The DHP is available upon request via the corresponding author of this paper.

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Chapter 6

Effects and moderators of exercise on quality of life and physical function in patients with cancer: an individual patient data meta-analysis of 34 RCTs

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Cancer treatment reviews. 2017; 52: 91-104

Abstract

This individual patient data meta-analysis aimed to evaluate the effects of exercise on quality of life (QoL) and physical function (PF) in patients with cancer, and to identify moderator effects of demographic (age, sex, marital status, education), clinical (body mass index, cancer type, presence of metastasis), intervention-related (intervention timing, delivery mode and duration, and type of control group), and exercise-related (exercise frequency, intensity, type, time) characteristics.

Relevant published and unpublished studies were identified in September 2012 via PubMed, EMBASE, PsycINFO, and CINAHL, reference checking and personal communications. Principle investigators of all 69 eligible trials were requested to share IPD from their study. IPD from 34 randomised controlled trials (n=4,519 patients) that evaluated the effects of exercise compared to a usual care, wait-list or attention control group on QoL and PF in adult patients with cancer were retrieved and pooled. Linear mixed-effect models were used to evaluate the effects of the exercise on post-intervention outcome values (z-score) adjusting for baseline values. Moderator effects were studies by testing interactions.

Exercise significantly improved QoL (β= 0.15, 95% CI= 0.10; 0.20) and PF (β= 0.18, 95% CI= 0.13; 0.23). The effects were not moderated by demographic, clinical or exercise characteristics. Effects on QoL ($\beta_{difference\_in\_effect}$= 0.13, 95% CI= 0.03; 0.22) and PF ($\beta_{difference\_in\_effect}$= 0.10, 95% CI= 0.01; 0.20) were significantly larger for supervised than unsupervised interventions.

In conclusion, exercise, and particularly supervised exercise, effectively improves QoL and PF in patients with cancer with different demographic and clinical characteristics during and following treatment. Although effect sizes are small, there is consistent empirical evidence to support implementation of exercise as part of cancer care.

Introduction

As a consequence of the increased number of cancer diagnoses, and concomitant mortality reductions for most types of cancer [1-3], many patients live with physical and psychosocial problems associated with the disease and its treatment that may compromise their quality of life (QoL). Exercise has been recommended as part of standard care for patients with cancer to help prevent and manage physical and psychosocial problems, and improve QoL [4, 5].

Previous meta-analyses of randomized controlled trials (RCT) reported benefits of exercise during and following cancer treatment [6]. Benefits include improved physical fitness, function, and quality of life (QoL), and reduced fatigue, and depression [6-9]. However, average reported effect sizes on these outcomes were small to moderate.

To maximize benefits of exercise, it is important to target subgroups of patients that respond best to a particular intervention [10]. A number of RCTs showed that demographic, clinical, and personal factors, such as age, marital status, disease stage and type of treatment, moderate the effects of exercise in patients with cancer [11-15]. However, these single studies are generally underpowered to analyze moderators of intervention effects and conduct subsequent stratified analysis. Meta-analyses based on aggregate data are limited to using summary data, such as the mean age of the patients or the proportion of men in a study, and they are unable to investigate intervention-covariate interactions at the level of the patient [16, 17].

Optimizing benefits of exercise also requires a better understanding of important intervention-related characteristics, including the timing and mode of intervention delivery, intervention duration, and exercise dimensions, in terms of frequency, intensity, type and time (FITT factors).

Meta-analyses of raw individual patient data (IPD) are suggested as the preferred method to evaluate moderators of intervention effects, since the large number of raw data points facilitates testing of interactions at the patient level, conducting subsequent stratified analyses, and standardizing analytic techniques across the included studies [18, 19]. In the current IPD meta-analysis we used data collected in the Predicting OptimaL Cancer RehabIlitation and Supportive care

(POLARIS) study [20]. The aims were to evaluate the effects of exercise on QoL and physical function (PF) in patients with cancer, and to identify demographic, clinical, intervention-, and exercise-related moderators of intervention effects.

Methods

The conduct and reporting of this IPD meta-analysis is based on the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) statement [21].

Identification and inclusion of studies

Detailed descriptions of the design and procedures of the POLARIS study were published previously [20]. In short, relevant published and unpublished studies (e.g. study protocol papers) were identified in September 2012 via systematic searches in four electronic databases (PubMed, EMBASE, PsycINFO, and CINAHL), reference checking of systematic reviews, meta-analyses, and personal communication with collaborators, colleagues, and other experts in the field [20]. POLARIS included RCTs that evaluated the effects of exercise interventions and/or psychosocial interventions on QoL compared to a wait-list, usual care or attention control group in adult patients with cancer. We excluded studies focusing on spiritual or existential therapy, yoga, and diet or multimodal lifestyle interventions. The study protocol was registered in PROSPERO in February 2013 (CRD42013003805) [20].

A letter of invitation to join the POLARIS consortium and share data was sent to the principal investigator (PI) of eligible RCTs. In case of no response, we sent reminders or contacted another PI. In case the study was not yet published, we maintained contact about the study completion date, to allow inclusion at a later stage during the data collection process of approximately 3 years. After PI's expressed interest in data sharing, they were requested to sign a data sharing agreement stating that they agreed with the POLARIS policy document, and were willing to share and transform anonymized data of study participants who were randomized. Data could be sent in various formats, were re-coded according to standardized protocols, and were checked for completeness, improbable values,

consistency with published articles, and missing items. Subsequently, datasets were imported into the POLARIS database where they were harmonized [20].

Data extraction and quality assessment

Two independent researchers (LB and MS) extracted study characteristics and rated the quality of included studies from published papers, using the 'risk-of-bias' assessment tool of the Cochrane Collaboration. The quality of following aspects was graded as high ('+'), low ('-') or unclear ('?') quality: random sequence generation (high quality if random component was used), allocation concealment (high quality if central, computerized allocation or sequentially numbered sealed envelopes were used), incomplete outcome (high quality if intention-to-treat analyses were performed and missing outcome data were <10% or adequate imputation techniques were used), and incomplete reporting (high quality if QoL or PF was reported such that data could be entered in an aggregate data meta-analysis). We also included ratings of adherence (high quality if ≥80% of patients had high attendance, defined as ≥80% of sessions attended [22, 23]) and contamination (high quality if no or limited exercise was present in the control group, i.e. moderate to vigorous exercise was present in <25% of patients or increased less than 60 minutes [24]). Items related to blinding were omitted because blinding of patients and personnel is difficult in the case of exercise interventions, and QoL and PF were assessed using patient-reported outcomes. Quality assessments of both reviewers were compared and disagreements in the scores were resolved by discussion.

Representativeness of included studies

To examine whether the included RCTs were a representative sample of all eligible RCTs, we compared pooled effect sizes of RCTs included versus those not included. Effect sizes per RCT were calculated by subtracting the published average post-intervention value of QoL or PF of the control group from that of the intervention group, and dividing the result by the pooled standard deviation. We corrected effect sizes for small samples as suggested by Hedges and Olkin. Effect sizes (Hedges' g) were pooled with a random effects model and differences in effects between studies providing data and those that did not were examined using Comprehensive

Meta-analysis software (version 2.2.064).

We evaluated publication bias for all eligible studies and for studies providing data by inspecting the funnel plot and by the Duval and Tweedie's trim and fill procedure [25, 26]. The procedure provides estimates of the number of missing studies and the effect size after the publication bias has been taken into account. The Egger's test was used to test whether the bias captured by the funnel plot was significant.

Outcome variables

QoL and PF were assessed with patient reported outcomes (PRO, Table 6.1). In the present paper, we used baseline (pre-intervention) and post-intervention values. To allow pooling of the different PROs, we recoded the individual scores into z-scores by subtracting the individual score from the mean score at baseline, and dividing the result by the mean standard deviation at baseline. Subsequently, the pooled z-scores were used for further analyses. If studies used both a cancer-specific and a generic QoL PRO, data from the cancer-specific PRO were used.

Possible moderators

Potential demographic and clinical moderators were identified from single studies that reported on the moderating effects with some inconsistent findings [11-14, 27].

Potential demographic moderators included baseline age, sex, marital status, and education level. Marital status was dichotomized into single versus married or living with partner. As a consequence of different coding schemes of the original RCTs, education level was dichotomized into low-medium (elementary, primary, or secondary school, lower or secondary vocational education) or high (higher vocational, college, or university education). Potential clinical moderators included body mass index (BMI), type of cancer, the presence of distant metastases, and type of treatment. BMI was categorized into underweight (<18.5 kg/m^2), normal weight (18.5-<25 kg/m^2), overweight (25-<30 kg/m^2) and obese (≥30 kg/m^2) according to the World Health Organization. The type of cancer was categorized into breast,

male genitourinary, gastrointestinal, hematological, gynecological, respiratory tract, and other types. Treatment with surgery, chemotherapy, radiotherapy, hormone therapy or stem cell transplantation were each dichotomized into previous or current treatment versus no such treatment. As the majority of men diagnosed with prostate cancer received androgen deprivation therapy, we were unable to study the moderating effects of hormone therapy in prostate cancer.

Timing of intervention delivery in relation to primary cancer treatment was categorized into pre-treatment, during treatment, post-treatment and end-of-life, according to the Physical Activity and Cancer Control (PACC) framework [28]. Because interventions pre-treatment and during end-of-life were not available, we tested differences in intervention effects between those delivered during treatment versus post-treatment. As hormone therapy for breast cancer may continue for five years post-treatment, we considered women on hormone therapy who completed other primary cancer treatments as being post-treatment. Men receiving androgen deprivation therapy for prostate cancer were considered as being during treatment. Delivery mode of intervention was dichotomized into supervised (in case (part of) the weekly exercise sessions were conducted under supervision) versus unsupervised (in case exercise sessions were performed unsupervised from or at home). Intervention duration was categorized based on tertiles (≤12 weeks; >12-24 weeks; >24 weeks). Exercise frequency was dichotomized based on the median, into ≤2 versus >2 supervised sessions per week for supervised exercise and into <5 versus ≥5 sessions per week for unsupervised exercise. Exercise intensity was categorized from low to high intensity using the definitions of the American College of Sports Medicine [29]. Exercise type was categorized into aerobic, resistance, combined aerobic and resistance and combined resistance and impact loading (e.g. skipping, jumping) exercise. Exercise time per session was categorized into ≤30 min, >30-60 min and >60 min.

Statistical analysis

We conducted one-step IPD meta-analyses to study the effects and moderators of exercise on QoL and PF. The effects were evaluated by regressing the intervention on the post-intervention value (z-score) of the outcome adjusted for the baseline value (z-score) using linear mixed model analyses with a two-level structure (1:

patient; 2: study) to take into account the clustering of patients within studies by using a random intercept on study level. Moderators of exercise effects were examined by adding the moderator and its interaction term with the intervention into the regression model, for each moderator separately. To reduce ecological bias for patient-level interactions, we separated within-trial interaction from between-trial interaction by centering the individual value of the covariate around the mean study value of that covariate [19]. If interaction terms were significant ($p<0.05$), stratified analyses were performed. In case a RCT had three study arms with different study-level moderators across study arms, interaction testing for a study-level moderator was not possible. Therefore, in those situations, we tested differences between subgroups using dummy variables. Regression coefficients and 95% confidence intervals (CI) were reported, which represent the between group difference in z-scores of QoL and PF, and correspond to a Cohen's d effect size. Effects of 0.2 were considered small, 0.50 as moderate and at or above 0.8 as large.

Since the majority of patients were women with breast cancer, we performed a sensitivity analysis to check robustness of findings in the subgroup of patients that were not women with breast cancer, despite non-significant overall interaction effects for women with breast cancer vs other (β= 0.09, 95% CI= -0.12; 0.29 for QoL; β= -0.06, 95% CI= -0.27; 0.14 for PF). Statistical analyses were performed using SPSS 22.0 and R Studio.

Results

Characteristics of studies and patients

Of the 136 RCTs that met the inclusion criteria (Figure 6.1), 66 evaluated the effects of exercise and three [30-32] evaluated the effects of a combined exercise and psychosocial intervention and also included a third arm with exercise only. Principal investigators of 34 of these 69 RCTs (response 49%) shared IPD. In total, 27 RCTs reported adequate random sequence generation, 26 studies reported adequate allocation concealment, 26 RCTs had adequate completeness of outcome data, and 26 RCTs had complete outcome reporting (Table 6.1). Intervention adherence was reported in 26 RCTs, and was of high quality in 13 RCTs, and 7 of the 13 RCTs that provided information on contamination met the criteria for high quality. The

Table 6.1. Descriptives of studies evaluating the effects of exercise on quality of life and physical function included in the database (n= 34), in alphabetical order of first author

					Intervention			Exercise	Control		Quality					
Author (year) Acronym	**Country**	**N**	**Age, mean (SD)**	**Gender (% female)**	**Diagnosis**	**Timing**	**Delivery mode**	**Duration (weeks)**	**FITT**		**PRO**	**RSG**	**AC**	**IO**	**IR**	**Adh**	**Con**
Arbane (2011) [52]	UK	51	64.0 (11.0)	48.1	Lung	Post	Unsupervised	12	F: ? I: moderate T: RE+AE T: ?	Usual care	C30	+	+	-	+	?	?
Cadmus, (2009) [53] IMPACT	USA	50	54.2 (9.6)	100	Breast	During	Unsupervised	26	F: aim 5x/week I: moderate T: AE T: 30 min	Usual care	FACT	+	+	+	+	-	?
Cormie (2015) [54]	AUS	64	67.9 (7.1)	0	Prostate	During ADT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	C30	+	+	+	+	?	?
Couneya (2003) [55] CANHOPE	CAN	93	60.3 (10.4)	41.9	Colorectal	During or post	Unsupervised	16	F: 3-5x/week I: moderate T: AE T: 20-30 min	Wait-list	FACT	+	?	+	+	-	-
Courneya (2003) [56] REHAB	CAN	52	58.6 (5.7)	100	Breast	Post	Supervised	15	F: 3x/week I: moderate-vigorous T: AE T: 15-35 min	Wait-list	FACT	+	+	+	+	+	+
Courneya (2007) [33] START	CAN	242	49.2 (9.3)	100	Breast	During CT	Supervised	Median: 17	F: 3x/week I: moderate-vigorous T: AE vs RE T: AE: 15-45 min	Usual care	FACT	+	+	+	+	-	+
Courneya (2009) [57] HELP	CAN	122	53.2 (14.8)	41.0	Hemato-logical	During or post	Supervised	12	F: 3x/week I: moderate-vigorous T: AE T: 15-45 min	Usual care	FACT	+	+	+	+	+	-

Table 6.1 (continued)

					Intervention				Exercise	Control		Quality					
Author (year) Acronym	**Country**	**N**	**Age, mean (SD)**	**Gender (% female)**	**Diagnosis**	**Timing**	**Delivery mode**	**Duration (weeks)**	**FITT**		**PRO**	**RSG**	**AC**	**IO**	**IR**	**Adh**	**Con**
Daley (2007) [58]	UK	108	51.1 (8.6)	100	Breast	Post	Supervised	8	F: 3x/week I: moderate-vigorous T: AE T: 50 min	Attention control vs usual care	FACT	+	+	+	+	-	-
Duijts (2012) [31] EVA	NL	207	47.8 (5.8)	100	Breast	Post	Unsupervised	12	F: 5x per 2 weeks* I: vigorous T: AE T: 45-60 min*	Wait-list	SF-36	+	+	-	+	-	?
Galvão (2010) [59]	AUS	57	69.8 (7.3)	0	Prostate	During ADT	Supervised	12	F: 2x/week I: moderate T: RE+AE T: 60 min	Usual care	C30	+	+	+	+	?	?
Galvão (2014) [60] RADAR-exercise	AUS	100	71.7 (6.4)	0	Prostate	Post ADT	Supervised	26	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care with PA brochure	C30	+	+	+	+	-	?
Goedendorp (2010) [32]	NL	144	57.2 (10.5)	63.2	Mixed	During	Home-based	Mean: 31.7	F: towards 5d/week I: ? T: AE T: towards 60 min	Usual care	C30	+	+	+	-	?	?
Griffith (2009) [61]	USA	126	60.2 (10.6)	38.9	Mixed	During CT, RT or both	Home-based	Mean: 12.8	F: 5x/week I: low-moderate T: AE T: 25-35min	Usual care	SF-36	?	?	+	-	-	-
Hayes (2013) [34] Exercise for Health	AUS	194	52.4 (8.5)	100	Breast	During and/or post	Unsupervised	35	F: aim: ≥ 4x/week I: moderate T: RE+AE T: 20-45 min	Usual care	FACT	+	+	+	+	+	-

Table 6.1 (continued)

						Intervention			Exercise	Control		Quality					
Author (year) Acronym	**Country**	**N**	**Age, mean (SD)**	**Gender (% female)**	**Diagnosis**	**Timing**	**Delivery mode**	**Duration (weeks)**	**FITT**		**PRO**	**RSG**	**AC**	**IO**	**IR**	**Adh**	**Con**
Herrero (2006) [62]	Spain	16	?	100	Breast	Post	Supervised	8	F: 3x/week I: moderate-vigorous T: RE+AE T: 90 min	Usual care	C30	?	+	-	-	+	?
Irwin (2009) [63] YES	USA	75	55.8 (8.7)	100	Breast	Post	Supervised	26	F: 3 supervised (+ 2 unsupervised) I: moderate T: AE (walking) T: 15-30 min	Usual care	FACT	+	?	-	+	-	+
Kampshoff (2015) [27] REACT	NL	277	53.5 (11.0)	80.1	Mixed	Post	Supervised	12	F: 2x/week I: moderate vs vigorous T: RE+AE T: 60 min	Wait-list	C30	+	+	+	+	-	+
Korstjens (2008) [30] OncoRev	NL	133	50.6 (10.2)	85	Mixed	Post	Supervised	12	F: 2x/week I: AE: moderate-vig-orous, RE: low-moderate T: RE+AE T: 120 min	Wait-list	C30	+	?	+	+	+	?
Mehnert (2011) [64]	GER	58	51.9 (8.5)	100	Breast	Post	Supervised	10	F: 2x/week I: moderate T: AE + gymnastics + movement games + relaxation T: 90 min	Wait-list	SF-36	?	+	+	-	+	?
Mutrie (2007) [65]	UK	201	51.6 (9.5)	100	Breast	During CT and/ or RT	Supervised	12	F: 2 supervised (+ 1 unsupervised) I: low-moderate T: RE+AE T: 45 min	Usual care	FACT	+	+	+	+	?	?

Table 6.1 (continued)

						Intervention			Exercise	Control		Quality					
Author (year) Acronym	**Country**	**N**	**Age, mean (SD)**	**Gender (% female)**	**Diagnosis**	**Timing**	**Delivery mode**	**Duration (weeks)**	**FITT**		**PRO**	**RSG**	**AC**	**IO**	**IR**	**Adh**	**Con**
Newton (2009) [66]	AUS	154	69.0 (9.0)	0	Prostate	During ADT	Supervised	24	F: 2x/week I: moderate-vigorous T: RE+AE vs RE+impact T: 60 min	Wait-list	C30	‡					
Ohira (2006) [67] WTBS	USA	86	52.7 (8.3)	100	Breast	Post	Supervised	26 (13 supervised)	F: 2x/week I: ? T: RE T: ?	Wait-list	Cares-SF	+	?	+	+	?	?
Persoon, (2010) [68] EXIST	NL	109	52.4 (11.2)	36.7	Haematological	Post SCT	Supervised	18	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	C30	‡					
Schmidt (2015) [69] BEATE	GER	88	52.5 (10.0)	100	Breast	During CT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE T: 60 min	Attention control	C30	+	+	+	+	-	?
Short (2015) [35] MM4L	AUS	330	55.9 (8.3)	100	Breast	Post	Unsupervised	16	F: AE: 5x/week; RE: 1-3x/week I: moderate T: RE+AE T: AE: 30 min	Usual care	FACT	+	+	+	+	+	?
Speck (2010) [70] PAL	USA	295	56.0 (8.8)	100	Breast	Post	Supervised	52 (13 supervised)	F: 2x/week I: ? T: RE T: 90 min	Wait-list	SF-36	+	+	-	+	+	?
Steindorf (2014) [71] BEST	GER	141	56.3 (8.9)	100	Breast	During RT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE T: 60 min	Attention control	C30	+	+	+	+	-	?

Table 6.1 (continued)

						Intervention			Exercise	Control		Quality					
Author (year) Acronym	**Country**	**N**	**Age, mean (SD)**	**Gender (% female)**	**Diagnosis**	**Timing**	**Delivery mode**	**Duration (weeks)**	**FITT**		**PRO**	**RSG**	**AC**	**IO**	**IR**	**Adh**	**Con**
Thorsen (2005) [72]	NOR	139	39.4 (8.3)	67.1	Mixed	Post	Unsupervised	14	F: 2x/week or more I: moderate-vigorous T: RE+AE T: 30 min or more	Usual care	C30	+	+	+	-	+	-
Travier (2015) [73]; van Vulpen (2015) [74] PACT	NL	237	50.7 (8.8)	100	Breast and colon	During CT	Supervised	18	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	C30	+	+	+	+	+	?
Van Waart (2015) [37] PACES	NL	253	51.4 (9.5)	95.7	Breast and Colon	During CT	Unsupervised vs supervised	Mean: 15.9	F: supervised: 2x/week; unsupervised towards 5x/week I: supervised: moderate-vigorous Unsupervised: moderate T: supervised: RE+AE; unsupervised: AE T: supervised: 60min; unsupervised: aim 30 min	Usual care	C30	+	+	+	+	-	?
Winters-Stone (2012) [75]	USA	106	62.2 (6.7)	100	Breast	Post	Supervised	52	F: 2x/week supervised (+ 1x/week unsupervised) I: moderate-vigorous T: RE+impact T: 60 min	Attention control	SF-36	+	+	+	+	+	+

Table 6.1 (continued)

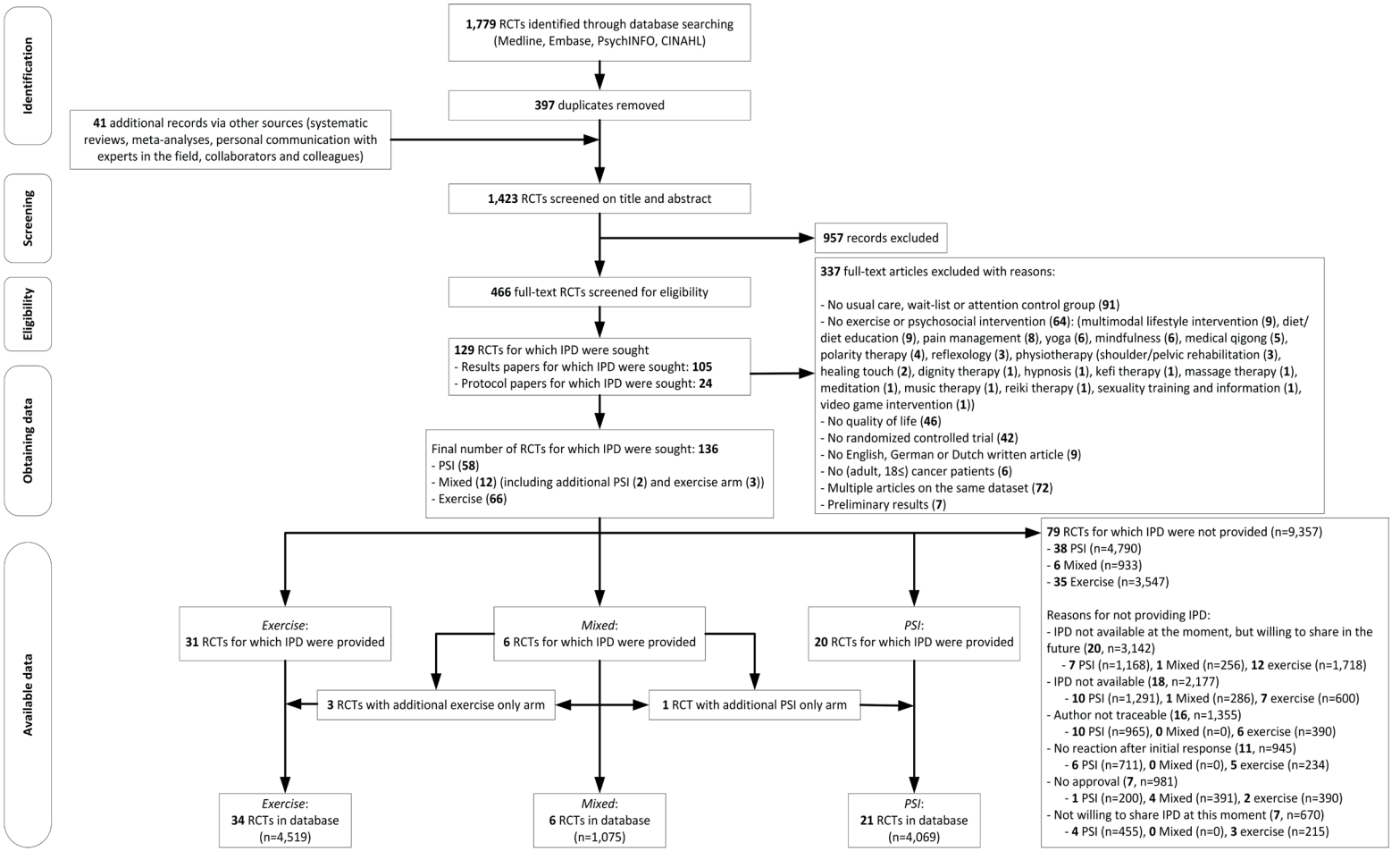
						Intervention			Exercise	Control		Quality					
Author (year) Acronym	**Country**	**N**	**Age, mean (SD)**	**Gender (% female)**	**Diagnosis**	**Timing**	**Delivery mode**	**Duration (weeks)**	**FITT**		**PRO**	**RSG**	**AC**	**IO**	**IR**	**Adh**	**Con**
Winters-Stone (2013) [76]	USA	71	46.4 (4.9)	100	Breast	Post	Supervised	52	F: 2x/week supervised + 1x/week unsupervised I: moderate T: RE+impact T: 60 min	Attention control	SF-36	+	+	+	-	-	+
Winters-Stone (2015) [77]	USA	51	70.1 (8.6)	0	Prostate	During ADT	Supervised	52	F: 2x/wk supervised (+ 1x/week unsupervised) I: moderate T: RE+impact T: 60 min	Attention control	C30	?	?	+	+	+	+
Wiskemann (2011) [78]	GER	80	48.4 (14.4)	31.3	Haemato-logical	Pre-during-post	Supervised	Median exercise: 16.4 Control: 15.7	F: 5x/week I: moderate-vigorous T: RE+AE T: AE: 20-40 min	Attention control	C30	+	+	-	+	+	?

* Personal communication with authors. ‡ quality rating could not be performed because papers are not yet published.

Abbreviations: ADT= androgen deprivation therapy; AE= Aerobic exercise training; CARES-SF= Cancer rehabilitation evaluation system short form; C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; CT= chemotherapy; FACT= Functional Assessment of Cancer Therapy; PRO= patient reported outcome; RE= Resistance exercise training; RT= radiotherapy; SF36= Short Form-36 Item Health Survey.

Quality assessment: + = high quality; - = low quality; ? = unclear quality; RSG= random sequence generation; AC= allocation concealment; IO=incomplete outcome; IR= incomplete reporting; Adh= adherence; Con= contamination.

Figure 6.1. Flow chart of study inclusion



IPD= individual patient data; PSI= psychosocial interventions; RCT= randomized controlled trial

sample included 4,519 patients with cancer, of whom 2,514 were randomized to the intervention group and 2,005 to the control group. The mean age was 54.6 (SD=11.3) years, 78% were women, 70% were diagnosed with breast cancer, 2% had metastatic disease, 51% exercised following cancer treatment, and 65% received supervised exercise (Table 6.2).

Representativeness and publication bias

Published summary data for QoL were available for 36 out of 69 RCTs, of which five [27, 33-36] included two exercise arms. Consequently, 41 exercise arms were included in the analyses of representativeness. For PF, summary data were published for 30 RCTs, with two [27, 37] evaluating two exercise arms, resulting in 32 exercise arms. We found no significant differences in effects on QoL (p=0.25) and PF (p=0.25) between RCTs of which IPD were shared and those of which were not (Table 6.3). The trim and fill procedures showed significant publication bias for all eligible RCTs reporting on QoL, but not between RCTs included and those not included (Table 6.3).

Table 6.2. Demographic, clinical, intervention-, and exercise-related characteristics, quality of life and physical function of patients in the exercise and control group

	Exercise (n=2,514)	Control (n=2,005)
Demographic		
Age, mean (SD) years	54.6 (11.5)	54.5 (11.2)
< 50 years	850 (33.8)	663 (33.1)
50-70 years	1405 (55.9)	1143 (57.0)
≥ 70 years	249 (9.9)	185 (9.2)
Unknown	10 (0.4)	14 (0.7)
Sex, n (%)		
Men	553 (22.0)	438 (21.8)
Women	1961 (78.0)	1567 (78.2)
Married/living with partner, n (%)		
Yes	1587 (63.1)	1209 (60.3)
No	442 (17.6)	389 (19.4)
Unknown	485 (19.3)	407 (20.3)

Table 6.2 (continued)

	Exercise (n=2,514)	Control (n=2,005)
Education level, n (%)		
Low/middle	1095 (43.6)	857 (42.7)
High	1018 (40.5)	728 (36.3)
Unknown	401 (16.0)	420 (20.9)
Clinical		
BMI, mean (SD) kg/m2	27.1 (5.1)	27.2 (5.3)
BMI categories, n (%)		
Underweight (BMI <18.5 kg/m2)	18 (0.7)	23 (1.1)
Normal weight (BMI 18.5 to < 25 kg/m2)	859 (34.2)	651 (32.5)
Overweight (BMI 25 to <30 kg/m2)	827 (32.9)	639 (31.9)
Obese (BMI ≥ 30 kg/m2)	551 (21.9)	450 (22.4)
Unknown	259 (10.3)	242 (12.1)
Cancer Type, n (%)		
Breast	1757 (69.9)	1406 (70.1)
Male genitourinary	326 (13.0)	248 (12.4)
Hematological	199 (7.9)	195 (9.7)
Gastrointestinal	146 (5.8)	87 (4.3)
Gynecological	44 (1.8)	33 (1.6)
Respiratory track	28 (1.1)	29 (1.4)
Other	14 (0.6)	7 (0.3)
Distant metastasis at baseline, n (%) [a]		
No	2241 (96.8)	1762 (97.3)
Yes	47 (2.0)	33 (1.8)
Unknown	27 (1.2)	15 (0.8)
Surgery, n (%) yes [b]		
No	299 (12.4)	242 (12.7)
Yes	1989 (82.3)	1552 (81.3)
Unknown	130 (5.4)	114 (6.0)
Chemotherapy, n (%)		
No	692 (27.5)	562 (28.0)
Prior to intervention	988 (39.3)	866 (43.2)
During intervention	761 (30.3)	513 (25.6)
Unknown	73 (2.9)	64 (3.2)
Radiotherapy, n (%)		
No	1030 (41.0)	760 (37.9)
Prior to intervention	1037 (41.2)	877 (43.7)
During intervention	364 (14.5)	314 (15.7)
Unknown	83 (3.3)	54 (2.7)

Table 6.2 (continued)

	Exercise (n=2,514)	Control (n=2,005)
Hormone therapy		
Breast cancer survivors (n= 3163), n (%)		
No	860 (48.9)	671 (47.7)
Yes	631 (35.9)	481 (34.2)
Unknown	266 (15.1)	254 (18.1)
Prostate cancer survivors (n= 536), n (%)	16 (5.2)	11 (4.8)
No	50 (16.2)	50 (21.9)
Prior to intervention	204 (66.2)	135 (59.2)
During intervention	38 (12.3)	32 (14.0)
Unknown		
SCT, n (%) [c]		
Allogeneic	42 (43.7)	42 (43.3)
Autologous	54 (56.3)	55 (56.7)
Intervention-related [d]		
Timing of intervention, n (%)		
Pre-during-post treatment	80 (1.8)	
During treatment	2122 (47.0)	
Post treatment	2314 (51.2)	
Mode of intervention delivery, n (%)		
(partly) Supervised	1643 (65.4)	
Unsupervised	871 (34.6)	
Duration of intervention, n (%)		
≤ 12 weeks	822 (32.7)	
12 - 24 weeks	683 (27.2)	
>24 weeks	741 (29.5)	
Unknown [e]	268 (10.7)	
Exercise frequency, n (%)		
2 times per week	1349 (53.7)	
3 times per week	323 (12.8)	
4 times per week	203 (8.1)	
≥5 times per week	509 (20.2)	
Unknown	130 (5.2)	
Exercise Intensity, n (%)		
Low	0 (0)	
Low-moderate	167 (6.6)	
Moderate	884 (35.2)	
Moderate-vigorous	1005 (40.0)	
High	195 (7.8)	
Unknown	263 (10.5)	

Table 6.2 (continued)

	Exercise (n=2,514)		Control (n=2,005)	
Exercise type, n (%)				
AE	686 (27.3)			
RE	385 (15.3)			
AE + RE	1270 (50.5)			
RE + Impact training	173 (6.9)			
Exercise session duration, n (%)				
≤ 30 min	928 (36.9)			
>30 – 60 min	1260 (50.1)			
>60 min	257 (10.2)			
Unknown	69 (2.7)			
Type of control group, n (%) [f]				
Usual care control			1265 (63.1)	
Wait list control			435 (21.7)	
Attention control			305 (15.2)	
Baseline values [g]	**Pre mean (SD)**	**Post mean (SD)**	**Pre mean (SD)**	**Post mean (SD)**
QoL, mean (SD)				
FACT-G, total score	81.3 (13.6)	85.6 (13.4)	82.2 (14.9)	84.3 (14.9)
EORTC QLQ-C30, subscale global QoL	70.4 (18.4)	73.2 (18.5)	68.8 (19.6)	69.0 (19.9)
CARES-SF, subscale global QoL	47.2 (9.3)	43.6 (9.0)	48.5 (9.1)	46.8 (9.5)
SF-36, subscale general health	66.4 (19.0)	69.5 (18.2)	66.6 (19.2)	68.3 (19.4)
PF, mean (SD)				
FACT-G, subscale PWB	21.9 (5.3)	23.7 (4.2)	22.2 (5.4)	23.2 (4.6)
EORTC QLQ-C30, subscale PF	84.1 (15.4)	85.0 (15.6)	82.7 (16.8)	80.8 (18.1)
CARES-SF, subscale PF	46.0 (7.4)	43.8 (5.7)	46.8 (6.8)	48.0 (7.7)
SF-36, subscale PF	82.7 (15.9)	85.0 (16.9)	82.9 (16.7)	82.4 (19.0)

Abbreviations: AE= aerobic exercise; CARES-SF= Cancer rehabilitation evaluation system short form; EORTC QLQ-C30= European Organisation Research and Treatment of Cancer Quality of life questionnaire-Core30; FACT= Functional Assessment of Cancer Therapy; FACT-G= FACT-General; PF= physical function; PWB= physical well-being; RE= resistance exercise; SCT= stem cell transplantation; SF-36= Short Form-36 Health survey. [a] proportion of survivors of solid tumors (n=4,124); [b] proportion of survivors without SCT (n=4,326); [c] proportion of survivors with SCT (n=193); [d] proportion of survivors from intervention groups (n=2,514); [e] Intervention duration of individual patients unknown for three studies, but mean or median was reported; [f] proportion of survivors from the control groups (n=2,005); [g] Scores are from 0-100 with higher scores representing higher QoL and PF for FACT-G, EORTC QLQ-C30 and SF-36, and lower QoL and PF for CARES-SF

Effects and moderators of exercise on QoL and PF

Exercise effects on QoL (β= 0.15, 95% CI= 0.10; 0.20) and PF (β= 0.18, 95% CI= 0.13; 0.23, Table 6.4, Figure 6.2) were significant. Patients' demographic and clinical characteristics, intervention timing and duration, and exercise FITT factors did not significantly moderate the effects on QoL or PF (Table 6.4). Supervised exercise had significantly larger effects on QoL ($\beta_{difference\_in\_effect}$= 0.13, 95% CI= 0.04; 0.23) and PF ($\beta_{difference\_in\_effect}$= 0.11, 95% CI= 0.01; 0.20) than unsupervised exercise. Compared to the control group, supervised exercise significantly improved both QoL (β= 0.20, 95% CI= 0.14; 0.25) and PF (β= 0.22, 95% CI= 0.16; 0.27), while unsupervised exercise significantly improved PF (β= 0.11, 95% CI= 0.03; 0.19). Effects on PF were significantly larger in RCTs with a usual care control group than those with an attention control group ($\beta_{difference\_in\_effect}$= 0.12, 95% CI= 0.002; 0.23).

Table 6.3. Representativeness and publication bias of the pooled effects of studies providing data for the POLARIS study and those not providing data

		Pooled effect	Test of heterogeneity			Between group differences
Representativeness	**N**	**g (95% CI)**	**Q**	**I^2**	**P-value**	**P value**
Quality of life						
All eligible studies	41	0.22 (0.14; 0.31)	71.96	44.42	0.001	
All eligible studies, excluding one outlier	40	0.18 (0.12; 0.24)	32.90	0.00	0.74	
Studies providing data	27	0.16 (0.09; 0.23)	22.22	0.00	0.68	
Studies not providing data	14	0.42 (0.17; 0.67)	45.06	71.15	<0.001	0.05
Studies not providing data, excluding one outlier	13	0.25 (0.12; 0.37)	9.35	0.00	0.67	0.25
Physical Function						
All eligible studies	32	0.32 (0.20; 0.44)	86.06	63.98	<0.001	
All eligible studies, excluding two outliers	30	0.27 (0.18; 0.35)	36.12	19.72	0.17	
Studies providing data	24	0.28 (0.19; 0.37)	30.87	25.50	0.13	
Studies not providing data	8	0.54 (0.05; 1.03)	53.44	86.70	<0.001	0.31
Studies not providing data, excluding two outliers	6	0.17 (-0.01; 0.34)	3.84	0.00	0.59	0.25

Table 6.3 (continued)

Publication bias using trim and fill procedure	$N_{missing}$	Adjusted effect	P_{Egger}
Quality of life			
All eligible studies, excluding one outlier	10	0.13 (0.07; 0.20)	0.02
Studies providing data	6	0.12 (0.05; 0.19)	0.20
Physical Function			
All eligible studies, excluding two outliers	3	0.29 (0.20; 0.37)	0.26
Studies providing data	2	0.31 (0.21; 0.40)	0.33

CI= confidence interval; g= Hedges' g effect size; I^2= I^2 statistic, which is the percentage of total variance that can be explained by heterogeneity, and 25% is considered low, 50% moderate, and 75% high heterogeneity; N= number of exercise intervention arms; Q= Q-test for heterogeneity, which is significant if there is evidence for heterogeneity

Sensitivity analyses among patients other than women with breast cancer (n=1,360, originating from 17 RCTs) showed slight differences in regression coefficients with larger confidence intervals, but the conclusions on moderator effects were similar.

Table 6.4. Effects and moderators of the effects of exercise on quality of life and physical function

	Quality of life β (95% CI)	Physical function β (95% CI)
Effect of exercise	0.15 (0.10; 0.20)*	0.18 (0.13; 0.23)*
Demographic moderators		
Interaction age categories		
< 50 years	Reference	Reference
50-70 years	0.06 (-0.06; 0.17)	-0.01 (-0.12; 0.10)
≥70 years	-0.06 (-0.28; 0.16)	-0.04 (-0.26; 0.17)
Interaction women vs. men	0.14 (-0.05; 0.32)	0.08 (-0.11; 0.26)
Interaction partner vs. single	-0.11 (-0.24; 0.02)	-0.07 (-0.22; 0.08)
Interaction high vs. low-middle education	-0.06 (-0.17; 0.05)	-0.01 (-0.12; 0.10)

Table 6.4 (continued)

	Quality of life β (95% CI)	Physical function β (95% CI)
Clinical moderators		
Interaction BMI categories		
Underweight (BMI <18.5 kg/m2)	0.28 (-0.24; 0.81)	0.28 (-0.15; 0.88)
Normal weight (BMI 18.5 to < 25 kg/m2)	Reference	Reference
Overweight (BMI 25 to <30 kg/m2)	-0.03 (-0.15; 0.09)	-0.03 (-0.06; 0.17)
Obese (BMI ≥ 30 kg/m2)	-0.02 (-0.16; 0.11)	-0.02 (-0.08; 0.19)
Interaction cancer type		
Breast	Reference	Reference
Male genitourinary	-0.25 (-0.58; 0.07)	0.02 (-0.31; 0.35)
Hematological	0.03 (-0.41; 0.47)	0.14 (-0.30; 0.59)
Gastrointestinal	0.23 (-0.09; 0.55)	0.08 (-0.24; 0.40)
Gynecological	0.10 (-1.00; 1.18)	0.45 (-0.66; 1.55)
Respiratory tract	0.06 (-0.40; 0.52)	0.03 (-0.43; 0.49)
Other	-0.43 (-1.65; 0.80)	-0.52 (-1.75; 0.72)
Interaction distant metastasis	-0.21 (-0.64; 0.22)	-0.06 (-0. 49; 0.37)
Interaction surgery	0.008 (-0.26; 0.28)	-0.05 (-0.32; 0.21)
Interaction chemotherapy	0.07 (-0.07; 0.22)	0.02 (-0.13; 0.16)
Interaction radiotherapy	-0.02 (-0.14; 0.10)	0.04 (-0.08; 0.16)
Interaction hormone therapy for breast cancer	-0.01 (-0.17; 0.14)	-0.07 (-0.23; 0.08)
Intervention-related moderators		
Interaction post vs. during treatment	0.02 (-0.08; 0.12)	0.04 (-0.39; 0.46)
Intervention delivery mode		
Effect supervised vs. unsupervised	0.13 (0.04; 0.23)*	0.11 (0.01; 0.20)*
Effect supervised vs. control	0.20 (0.14; 0.25)*	0.22 (0.16; 0.27)*
Effect unsupervised vs. control	0.06 (-0.02; 0.14)	0.11 (0.03; 0.19)*
Interaction Intervention duration		
≤ 12 weeks	Reference	Reference
12 – 24 weeks	-0.19 (-0.32; -0.07)* [a]	-0.12 (-0.24; 0.00)# [a]
>24 weeks	-0.09 (-0.21; 0.03)	-0.05 (-0.16; 0.07)
FITT factors for supervised exercise		
Frequency		
Interaction 3 times/week vs. 2 times/week	0.04 (-0.10; 0.18)	0.01 (-0.12; 0.15)
Intensity		
Effect low-moderate and moderate vs. control	0.23 (0.12; 0.34)*	0.22 (0.12; 0.33)*
Effect moderate-vigorous and vigorous vs. control	0.21 (0.13; 0.28)*	0.22 (0.15; 0.29)*
Effect moderate-vigorous and vigorous vs. low-moderate and moderate	-0.03 (-0.15; 0.10)	-0.007 (-0.13; 0.11)

Table 6.4 (continued)

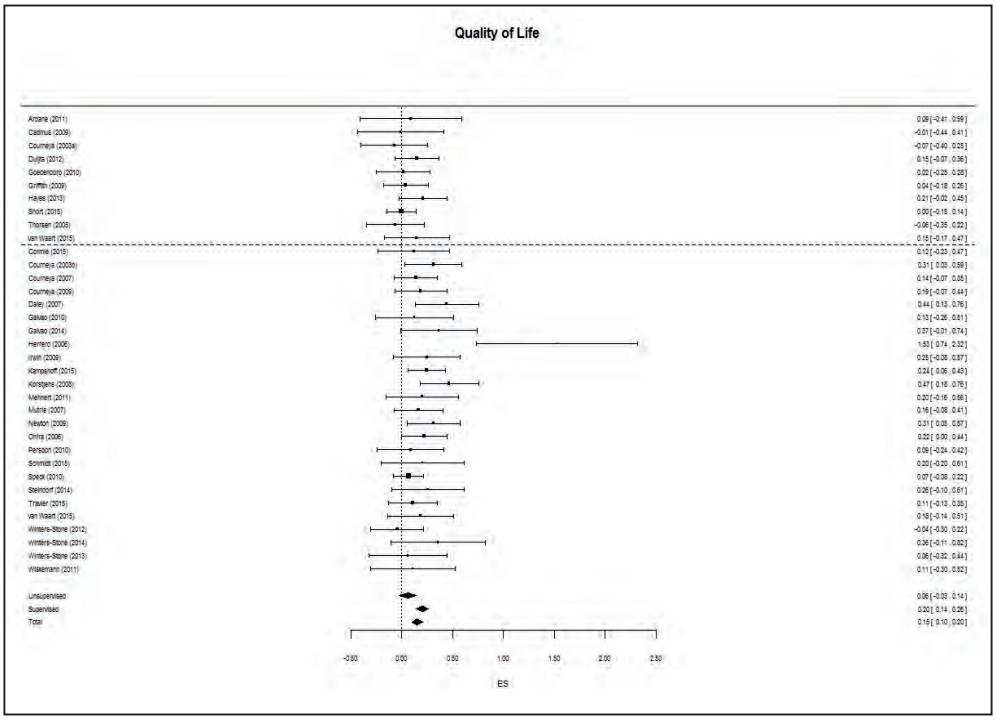
	Quality of life β (95% CI)	Physical function β (95% CI)
Type [b]		
Control	Reference	Reference
AE	0.25 (0.13; 0.38)*	0.21 (0.10; 0.34)*
AE+RE	0.21 (0.13; 0.30)*	0.22 (0.14; 0.30)*
RE	0.15 (0.04; 0.26)*	0.26 (0.16; 0.37)*
RE + impact training	0.16 (-0.02; 0.34)	0.16 (-0.02; 0.34)
Time of session	0.03 (-0.12; 0.19)	-0.05 (-0.20; 0.10)
Interaction >30–60 min vs. 0 – 30 min	0.10 (-0.10; 0.29)	0.02 (-0.17; 0.20)
Interaction > 60 vs. 0–30 min	0.06 (-0.10; 0.23)	0.07 (-0.09; 0.23)
Interaction > 60 min vs. >30–60 min		
FITT factors for unsupervised exercise		
Frequency	-0.06 (-0.24; 0.12)	-0.01 (-0.20; 0.18)
Interaction ≥5 times/week vs. <5 times/week		
Intensity	0.003 (-0.20; 0.21)	0.09 (-0.14; 0.31)
Interaction moderate-vigorous and vigorous vs. low-moderate and moderate		
Type	-0.01 (-0.18; 0.16)	-0.17 (-0.36; 0.01)#
Interaction RE+AE vs. AE		
Time	0.18 (-0.02; 0.37)#	0.14 (-0.08; 0.37)
Interaction > 30 min vs. ≤30 min		

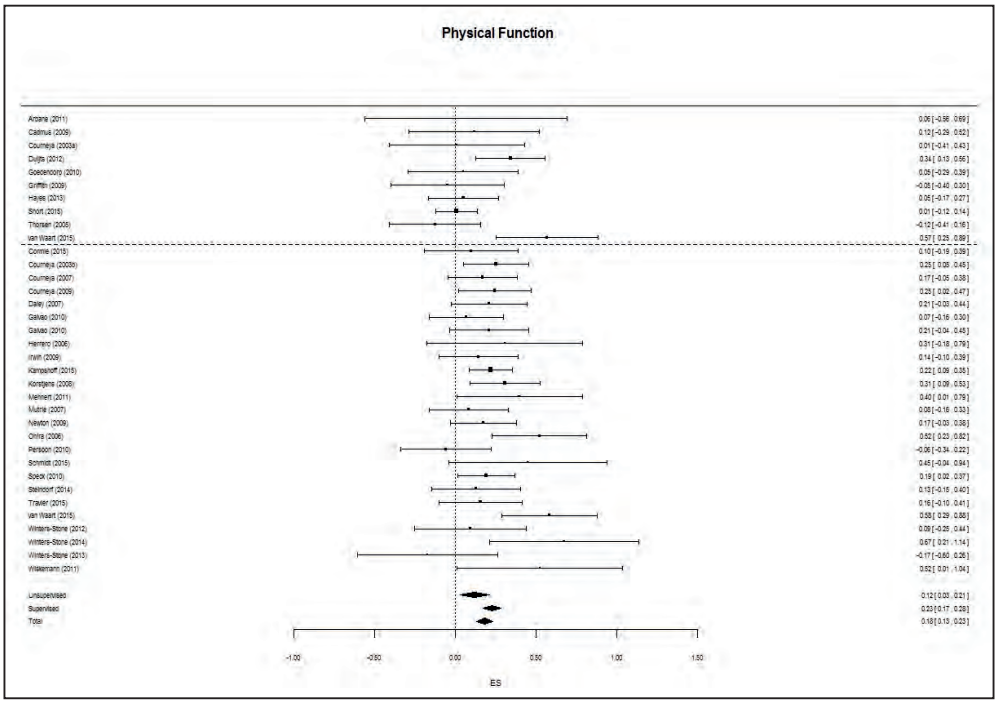
* p<0.05; # 0.05≤p<0.10; [a] Interaction term not significant after adjusting for delivery mode; [b] Significantly larger effects of AE, AE + RE and RE than the control group, no significant differences in effects between different exercise types. Abbreviations: AE= aerobic exercise; BMI= body mass index; CI= confidence interval; RE= resistance exercise

Discussion

Based on IPD meta-analyses of 34 RCTs including data from 4,519 individual patients with cancer, we found that exercise significantly improved their QoL and PF. The IPD meta-analytical approach of the present paper enabled the testing of potential moderators in a large sample. The exercise effects did not differ significantly across subgroups of age, sex, education level, marital status, BMI, cancer type, metastatic stage or treatment. Further, exercise was equally effective during and following cancer treatment. These findings support and strengthen the evidence base for current exercise recommendations that all patients with cancer should be physically

Figure 6.2. Forest plots of the effects of exercise on quality of life (a) and physical function (b).





active during and following cancer treatment [4]. However, the effects were stronger for supervised exercise. We found no significant moderating effects of intervention timing, duration, and exercise FITT factors.

The exercise effects were significant, but small in general, and comparable across the different subgroups. The lack of demographic and clinical moderators suggests that targeting exercise, based on demographic and clinical characteristics may not be useful for improving QoL and PF.

The moderating effects of sex, age, education, marital status, BMI and cancer type have been explored in previous single studies reporting inconsistent findings [11-14, 27]. It has been hypothesized that patients without a partner have less social support at home [38, 39] and may therefore either benefit more from the support associated with supervised or guided exercise [13, 14], or may be less likely to adhere to the exercise intervention [23]. We analyzed the potential moderating effect of being married/having a partner, although this does not necessarily reflect partner support, and found no moderator effect on QoL and PF.

Additionally, we found no moderator effect of BMI. However, due to the higher likelihood of sarcopenic obesity (i.e. increased fat mass in combination with reduced muscle mass) caused by cancer and its treatment [40], BMI may not adequately reflect adiposity in patients with cancer. Additional studies are needed to investigate the moderator effects of muscle and fat mass.

We found no significant differences in effects on QoL and PF across cancer types or between patients with metastatic and non-metastatic disease. However, sample sizes of some subgroups were small, and due to different coding schemes or lack of information on disease stage we were limited to studying differences in intervention effects between patients with metastatic and non-metastatic disease, and were unable to further disentangle differences in effects between patients with disease stages I, II and III. Furthermore, the majority of studies evaluating the effects of exercise have been conducted in patients with breast cancer, and prostate cancer who were treated with curative intent [4, 7]. Therefore exercise effects on QoL and PF remain unclear in understudied cancer populations, such as head and neck, lung, and gynecological cancers, and in patients with metastatic disease, and they may differ from those with breast and prostate cancer due to differences in treatment trajectories. We were unable to confirm previous findings

that radiotherapy [12] or chemotherapy [13] moderate exercise effects, which may be related to the heterogeneous study population. As treatment types are related to cancer types, the moderator effects of treatment should perhaps be investigated separately within each cancer type.

Intervention goals are likely to differ across phases of the cancer continuum. Exercise during cancer treatment typically seeks to influence treatment effectiveness and coping by managing side effects, maintaining physical fitness, and preventing muscle loss, fat gain, fatigue, and deterioration in QoL [28]. Exercise post-treatment typically aims to speed recovery, improve physical fitness and QoL, reduce fatigue, distress and the risk of developing chronic diseases or secondary cancers [28]. Nevertheless, the exercise effects on QoL and PF were similar, and clearly demonstrate significant benefits both during and post cancer treatment, which is consistent with previous meta-analyses based on aggregate data [6, 8, 9].

Effects of supervised exercise were twice as large as those of unsupervised exercise, which is consistent with a previous systematic review [41]. The larger effects of supervised exercise may be explained by the attention of the physiotherapist or exercise physiologist delivering the intervention, access to better equipment, more challenging exercise prescriptions, or by better adherence to the prescribed exercise protocol. Reporting adherence and identifying determinants of adherence to unsupervised interventions is important to identify patients who do not need supervision.

The lack of significant differences in exercise effects across different FITT factors might have resulted from little variation in these factors across studies, or the limited power since FITT factors are moderators at the intervention level instead of the patient level. Previous head-to-head comparisons of exercise FITT factors indicated a dose response effect of aerobic exercise on PF during cancer treatment in patients with breast cancer [42] and larger effects of high intensity compared to moderate intensity exercise post treatment in a population with mixed cancer types [27]. More RCTs that directly compare exercise FITT factors are warranted to define optimal exercise prescriptions. Also, specific intervention components, including goal-setting, social support and exercise instructions and monitoring, may differ across interventions, and explain differences in effects.

The effects on QoL and PF were significant, but smaller than expected. There

may be several explanations for the smaller effects. First, exercise interventions generally aim to improve exercise behavior or health-related physical fitness, and probably not all dimensions of QoL (i.e. physical, emotional and social well-being) [43] were affected to the same extent. Second, QoL is susceptible to response shift [44, 45], i.e., a change in the meaning of one's self-evaluation of QoL over time as a result of changes in internal standards, values and the conceptualization of QoL [46]. Third, results may have been contaminated by the adoption of exercise by patients in the control group. The limited information on contamination hampered us to evaluate its influence on the effects. Fourth, our analyses were based on patients participating in RCTs. Median (interquartile range) participation rates in exercise trials were found to be 63% (33-80) of eligible patients [47]. Patients who decline participation may be less motivated for exercise and have lower exercise levels, thus we may not reach patients who may benefit the most. However, studies comparing exercise of participants and non-participants found no differences [23, 48, 49]. Nevertheless, demographics may differ between participants and nonparticipants, with the latter more likely to be older [48] and to have lower education levels [23, 49]. Therefore, results may not be fully generalizable to all patients with cancer. Future IPD meta-analyses should also study the moderator effects of baseline QoL, PF and fitness [50], and specific symptoms as fatigue and distress [12] and the moderator effects on other physical, psychosocial and clinical outcomes, as they may differ [13, 14].

Study strengths are the large number of included RCTs from multiple countries, the consequent large sample size, and the uniform analytical procedures across all studies. Limitations are the following: first, there was considerable publication bias in studies that met our inclusion criteria, overestimating the intervention effects, particularly for studies reporting on QoL. However, no significant differences in effect sizes were found between studies providing data and those that did not, indicating that the 34 RCTs included in the analyses were a representative sample of the published literature. Second, not all RCTs met all quality criteria. In particular, information on exercise adherence and contamination was limited, hampering the ability to check whether adherence was similar across moderator subgroups. However, a previous review on determinants of exercise adherence in patients with cancer concluded that the majority of studies showed no significant association of demographic and clinical factors with adherence [51]. Finally, we focused on short term intervention effects as very few studies have

examined maintenance of intervention effects into the long term.

In conclusion, exercise, and particularly those with a supervised component, effectively improves QoL and PF across subgroups of patients with cancer with different demographic and clinical characteristics, both during and following treatment. Although effect sizes were small, our study provides additional evidence to support the implementation of exercise as part of standard care to improve QoL and PF. Current knowledge on the exercise effects on QoL and PF is primarily based on studies in patients with non-metastasized breast or prostate cancer. Future studies should therefore shift the focus to understanding the exercise effects in understudied and advanced cancer populations; on clinical outcomes including specific symptoms, cancer treatment completion, and survival; and on how to optimize exercise participation, adherence, and prescriptions.

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Chapter 7

Effects and moderators of psychosocial interventions on quality of life, and emotional and social function in patients with cancer: an individual patient data meta-analysis of 22 RCTs

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Psycho-Oncology. 2018; 27 (4): 1150-1161

Abstract

Objective: This individual patient data (IPD) meta-analysis aimed to evaluate the effects of psychosocial interventions (PSI) on quality of life (QoL), emotional function (EF) and social function (SF) in patients with cancer, and to study moderator effects of demographic, clinical, personal, and intervention-related characteristics.

Methods: Relevant studies were identified via literature searches in four databases. We pooled IPD from 22 (n=4,217) of 61 eligible randomized controlled trials (RCTs). Linear mixed-effect model analyses were used to study intervention effects on the post-intervention values of QoL, EF, and SF (z-scores), adjusting for baseline values, age, and cancer type. We studied moderator effects by testing interactions with the intervention for demographic, clinical, personal, and intervention-related characteristics, and conducted subsequent stratified analyses for significant moderator variables.

Results: PSI significantly improved QoL (β= 0.14, 95% confidence interval (CI)= 0.06; 0.21), EF (β= 0.13, 95% CI= 0.05; 0.20), and SF (β= 0.10, 95% CI= 0.03; 0.18). Significant differences in effects of different types of PSI were found, with largest effects of psychotherapy. The effects of coping skills training (CST) were moderated by age, treatment type, and targeted interventions. Effects of psychotherapy on EF may be moderated by cancer type, but these analyses were based on two RCTs with small sample sizes of some cancer types.

Conclusions: PSI significantly improved QoL, EF, and SF, with small overall effects. However, the effects differed by several demographic, clinical, personal, and intervention-related characteristics. Our study highlights the beneficial effects of CST in patients treated with chemotherapy, the importance of targeted interventions, and the need of developing interventions tailored to the specific needs of elderly patients.

Introduction

Previous systematic reviews and meta-analyses from randomized controlled trials (RCTs) have reported that psychosocial interventions (PSI) significantly reduce psychosocial problems and improve the quality of life (QoL), emotional function (EF), and social function (SF) of patients during and after cancer treatment, but effects sizes vary [1-13]. Better insight into intervention moderators can facilitate identifying and subsequently targeting subgroups of patients with cancer that respond best to a particular type of PSI, thereby improving the intervention effects [14].

Results from individual RCTs have suggested that younger age, female gender, lower socio-economic status, having breast cancer compared to lung cancer, cancer recurrence, lower self-esteem, higher depressive symptoms, and lower self-efficacy moderate the effects of PSI in patients with cancer [15-19]. However, these findings from individual RCTs should be interpreted with caution as they are generally not designed and powered to study moderators of intervention effects [20].

Additionally, meta-analyses on aggregate (summary) data from RCTs have shown that the effects of PSI on psychological well-being were larger in patients with older age, male gender, lower income, and other types of cancer compared to breast cancer [6]. Larger effects have also been reported for patients with higher distress and lower QoL at baseline, and who attended a psychotherapeutic or psycho-educational intervention compared to an information-only intervention [1, 2, 4, 5, 7, 12]. However, a meta-analysis of summary data relies on mean patient characteristics (e.g. the mean age of patients or the proportion of women in a study), which does not allow testing of interactions between the intervention and patient-level characteristics [20]. The use of summary data thereby increases the risk for ecological bias, which refers to the failure of associations at the study-level to correctly reflect associations at the patient-level caused by confounding factors across trials [21]. Moderator effects found in aggregate data meta-analyses should therefore be interpreted with caution.

A meta-analysis of individual patient data (IPD) involves obtaining and then synthesizing the raw IPD from multiple related studies [22], and has the advantage to test interactions between interventions and patient-level characteristics using

the large number of raw data points, conducting subsequent stratified analyses, and standardized analytic techniques across the included studies [23, 24].

The current IPD meta-analysis is part of the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study [25]. The aims were to evaluate the effects of PSI on QoL, EF, and SF in patients with cancer, and to identify for the first time demographic, clinical, personal, and intervention-related moderators of intervention effects with IPD meta-analysis.

Methods

Identification and inclusion of studies

Detailed descriptions of the design, procedures, and search strategies of the POLARIS study have been published previously [25]. Briefly, relevant published and unpublished studies (e.g. study protocol papers) were identified via systematic searches in four electronic databases (PubMed, EMBASE, PsycINFO, and CINAHL), reference checking of systematic reviews, meta-analyses, and personal communication with collaborators, colleagues, and other experts in the field [25]. The original search was conducted in September 2012 [25]. In case an identified study was not yet published, we maintained contact about the study completion date, to allow inclusion at a later stage during the data collection process of approximately 3 years. POLARIS included RCTs that evaluated the effects of physical activity interventions and/or PSI on QoL compared to a wait-list, usual care or attention control group in adult patients with cancer [25]. The effects of physical activity interventions on QoL and physical function have been reported elsewhere [26].

We used Cunningham's hierarchic classification to distinguish five types of heterogenetic PSI, based on the degree of psychological change that the different interventions aim to promote in patients with cancer: (I) information provision, i.e. interventions aiming to increase a patient's knowledge of cancer and/or its treatments, side effects, and consequences; (II) support, i.e. interventions intended to help patients to cope with the implications of cancer and its treatment, e.g. express associated emotions, diminish a sense of isolation, identify unmet needs, take some control over events, deal with family members and health care personnel, and accept

losses and changed roles; (III) coping skills training (CST), i.e. interventions targeted at attaining new cognitive-behavioral skills such as relaxation, mental imaging, thought and affect management, and activity planning; (IV) psychotherapy, i.e. interventions delivered by an appropriately trained professional which aim to achieve a more fundamental psychological change to increase self-understanding via, for example, psychodynamic therapy, and supportive-therapeutic approaches; and (V) spiritual or existential therapy, i.e. interventions promoting experiential awareness of a transcendent order or power, some sense of belonging to a meaningful universe including mediation and prayer (where meaningful to the patient), appropriate reading, discussion, and reflection around spiritual topics [27].

For the current IPD meta-analysis, RCTs on PSI that fit in the first four categories were included. Although we acknowledge the potential importance of the fifth category, we excluded RCTs focusing on PSI in this category, because of the heterogeneity of RCTs on PSI in this category (e.g. spiritual or existential therapy, including meditation and mindfulness). At this point, we also excluded interventions such as yoga and pain management, as well as diet or multimodal lifestyle interventions (for example physical activity and diet combined), to reduce heterogeneity, and to keep the number of datasets to be retrieved manageable. Based on the description of the intervention provided in the original studies, two authors (JK+IVdL) independently classified the type of intervention. Disagreements (9%) were resolved by discussion. All PI's of original studies approved the categorization. The study protocol was registered in PROSPERO in February 2013 (CRD42013003805) [25].

A letter of invitation to join the POLARIS consortium and share data was sent to the principal investigator (PI) of eligible RCTs. In case of no response, we sent reminders or contacted another PI on the same study. After PI's expressed interest in data sharing, they were requested to sign a data sharing agreement stating that they agreed with the POLARIS policy document, and were willing to share anonymized data of study participants who were randomized. The data could be supplied in various formats, and were checked for completeness, improbable values, consistency with published articles, and missing items. Subsequently, data sets were imported in the POLARIS database where they were re-coded according to standardized protocols and harmonized [25].

Representativeness of included studies

To examine whether the included RCTs were a representative sample of all eligible RCTs, we compared pooled effect sizes of RCTs included with those not included. For this purpose, we updated the original search in October 2017 to also include studies that were published recently. Effect sizes per RCT were calculated by subtracting the published average post-intervention value of QoL, EF, or SF of the control group from that of the intervention group, and dividing the result by the pooled standard deviation. We adjusted effect sizes for small samples as suggested by Hedges and Olkin [28]. Effect sizes (Hedges'g) were pooled with a random effects model and differences in effects between studies providing data and those that did not were examined using Comprehensive Meta-analysis software (version 2.2.064).

We evaluated publication bias for all eligible studies and for studies providing data by inspecting the funnel plot and by the Duval and Tweedie's trim and fill procedure [29, 30]. The procedure provides estimates of the number of missing studies and the effect size after the publication bias has been taken into account. The Egger's test was used to test whether the bias captured by the funnel plot was significant.

Data extraction and quality assessment of included studies

Two independent researchers (JK+MS) extracted study characteristics and rated the quality of included studies from the published papers. We used the recommended "risk of bias" assessment tool of the Cochrane Collaboration [31] to grade the quality as high ('+'), low ('-'), or unclear (?) on the following aspects: random sequence generation (high quality if a random assignment was used), allocation concealment (high quality in case of central, computerized allocation or sequentially numbered sealed envelopes), incomplete outcome (high quality if intention-to-treat analyses were performed, and less than 10% of the outcome data were missing or adequate imputation techniques were used), and incomplete reporting (high quality if all pre-specified outcomes were reported such that they could be entered in an summary data meta-analysis). In addition, we included ratings of adherence (high quality if ≥80% of patients had high attendance, defined as ≥80% of sessions attended) and contamination (high quality if no or limited adoption (<20%) of the intervention

in the control group) as other potential sources of bias. Items related to blinding were omitted because blinding of patients and personnel is difficult in case of a PSI. Also the rating of blinding of outcome assessors was excluded because QoL, EF and SF were assessed using patient-reported outcomes (PROs). Quality assessment of both reviewers were compared and disagreements were resolved by discussion and consulting a third researcher (LB).

Outcome variables

QoL, EF, and SF were assessed with PROs (Table 7.2). In the present paper, we used baseline (pre-intervention) and immediate or closest to post-intervention values of the outcomes. Although we acknowledge the importance of long-term intervention effects, this paper focuses on direct (short-term) effects of the intervention, because follow-up data was provided for only half of the studies which also used different follow-up durations. To allow pooling of the different PROs, we recoded the individual scores into z-scores by subtracting the mean score at baseline from the individual score, then dividing the result by the mean standard deviation at baseline. Subsequently, the pooled z-scores were used for further analyses. If studies used both a cancer-specific and a generic QoL PRO, data from the cancer-specific PRO were used.

Possible moderators

The potential moderators tested in this IPD meta-analysis were identified from previous original RCTs or meta-analyses [1, 2, 6, 7, 16, 19, 32, 33]. Potential demographic moderators included age, sex, marital status, and education level. We dichotomized marital status into single and/or living alone versus married and/or living with partner. As a consequence of different coding schemes used in the original RCTs, education level was dichotomized into low-medium (primary or secondary school, and lower or secondary vocational education) or high (higher vocational, college, or university education).

Potential clinical moderators included type of cancer, type of treatment, and the presence of distant metastases. The type of cancer was categorized into breast,

male genitourinary, gastrointestinal, hematological, gynecological, respiratory tract, and other types. We also checked moderator effects of breast cancer versus other types of cancer. Treatment with surgery, chemotherapy, radiotherapy, or hormone therapy were each dichotomized into previous or current treatment versus no such treatment. Personal moderators included baseline values of QoL, EF, and SF (z-scores).

Intervention type was categorized into information, support, CST, or psychotherapy, according to the classification model of Cunningham et al [27]. Timing of intervention delivery was categorized into pre- anti-cancer treatment, during treatment, post-treatment, and end-of-life [34]. As studies on interventions delivering PSI pre-treatment and during end-of-life were not available, and only one study delivered PSI both pre-and post-treatment, we tested differences in intervention effects between those delivered during and post-treatment. As hormone therapy for breast cancer may continue for several years post-treatment, we considered women on hormone therapy who completed other primary cancer treatments as being post-treatment. Men receiving androgen deprivation therapy for prostate cancer were considered as being during treatment. Intervention duration was dichotomized based on the median (≤12 weeks; >12 weeks). Interventions targeting patients with distress (e.g. depression, fatigue, cognitive problems, symptoms) were dichotomized into yes or no.

Statistical analysis

We conducted one-step IPD meta-analyses to study the effects and moderators of PSI on QoL, EF and SF. The effects were evaluated by regressing the post-intervention value (z-score) of the outcome onto the intervention using linear mixed model analyses with a two-level structure (patients as level one and study as level two) to take into account the clustering of patients within studies by using a random intercept on study level. The baseline value of the outcome (z-score), age and cancer type were included in the model as covariates. The residuals of the models were distributed normally. Moderators of the intervention effects were examined by adding the moderator and its interaction term with the intervention into the regression model, for each moderator separately. To reduce ecological bias for patient-level interactions, we separated within-trial interaction from between-

trial interaction by centering the individual value of the covariate around the mean study value of that covariate [24]. In case a RCT had three study arms with different study-level moderators across study arms, interaction testing for a study-level moderator was not possible. Therefore, in those situations, we tested differences between subgroups using dummy variables.

If the likelihood ratio test of the model with and without interaction term was significant ($p<0.05$), strata were built, and the moderator analyses were repeated in the strata that included data from more than one RCT. Because type of intervention was the most significant moderator, we re-examined the other potential moderators of intervention effects within the strata based on type of intervention (CST and psychotherapy). Since the majority of patients were women with breast cancer that followed CST, we performed a sensitivity analysis in this subgroup of patients.

Regression coefficients and 95% confidence intervals (CI) were reported, which represent the between group difference in z-scores of QoL, EF, and SF, and correspond to a Cohen's d effect size. According to Cohen [35], d=0.2 was considered small, d=0.5 medium, and d=0.8 large, respectively. The statistical analyses were conducted in SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and RStudio [36].

Results

Characteristics of studies and patients

Of the 136 RCTs that met the inclusion criteria for the POLARIS study in the original search, 59 RCTs evaluated the effects of PSI, and 2 RCTs [37, 38] that evaluated the effects of physical activity combined with PSI also included a third study arm with PSI only (Figure 7.1). PI's of 22 of the 61 eligible RCTs (response 36%) [37, 39-59], shared their data. In one RCT focusing on hematological cancer [41], we excluded patients who followed watchful waiting only (n=23), as they did not fit into one of the intervention categories. In one RCT that included patients with mixed cancer types [50], we excluded patients with gastrointestinal cancer as they received PSI combined with nutritional support (n=140). The final dataset included 4,217 patients with cancer of whom 2,215 were randomly allocated to the intervention

Table 7.1. Characteristics of the 22 included randomized controlled trials on the effect of psychosocial interventions, in alphabetical order of first author

						Intervention								Con.	Quality						
Author (year)	Country	N	Age, mean	Sex (% male)	Diagnosis	Timing	Targeted	Type	Format	Method	Duration	Sessions	Proession		PRO (P or S)	RSG	AC	IO	IR	Adh	Con
Armes, 2007	UK	55	40	59	Mixed	During CT	Yes	CST	Individual	FTF	12	3	Nurse	UC	QLQ-C30 S	+	+	+	+	-	?
Arving, 2007	SWE	179	0	55	Breast	During	No	CST	Individual	FTF	4	NR	Nurse or psychologist	UC	QLQ-C30 P	+	?	+	+	?	?
Braamse, 2015	NL	72	72	54	Hema	Post high-dose CT and auto-SCT	No	CST	Individual	Web	13	NR	Psychologist	UC	QLQ-C30 S	+	+	+	+	-	+
Chambers, 2013	AUS	740	100	61	Prostate	Pre and post	No	CST	Individual	Tel	8	5	Nurse	UC	SF-36 P	+	+	+	+	+	?
Duijts, 2012	NL	212	0	48	Breast	Post CT and/or HT	Yes	CST	Group	FTF	12	6	Psychologist	WLC	SF-36 S	+	+	+	+	-	?
Ell, 2008	USA	472	16	49	Mixed	During or post	Yes	PT	Individual	FTF	52	0 – 54	Cancer depression clinical	AC	FACT-G P	+	+	+	+	-	?
Ferguson, 2012	USA	40	0	50	Breast	Post CT	Yes	CST	Individual	FTF	8	4	Psychologist	WLC	QOL-CS P	+	+	+	+	?	?
Gellaitry, 2010	UK	93	0	58	Breast	Post RT	No	CST	Individual	Tel	4	4	Researcher	UC	FACT-G P	+	?	-	-	?	?
Gielissen, 2006	NL	98	51	45	Mixed	Post	Yes	CST	Individual	FTF	26	5 – 26	Psychologist	WLC	QLQ-C30 S	?	+	+	+	?	?
Goedendorp, 2010	NL	148	36	56	Mixed	During	No	CST	Individual	FTF	26	1-10	Psychologist	UC	QLQ-C30 S	+	+	+	-	?	?
Graves, 2003	USA	32	0	56	Breast	During or post	No	CST	Group	FTF	8	8	Psychologist	UC	FACT-G P	?	?	-	-	?	?
Heiney, 2003	USA	66	0	50	Breast	Post	No	CST	Group	Tel	6	6	Group ther-apist	UC	QOL-CS P	+	?	-	+	+	?
Johansson, 2008	SWE	171	35	62	Breast & Prostate	During	No	CST	Individual	FTF	12	1 – 24	Psychologist	UC	QLQ-C30 P	+	+	?	+	?	?
Kimman, 2011	NL	299	0	56	Breast	Post	No	Info	Group	FTF	12	2	Psychologist	UC	QLQ-C30 P	+	+	+	+	+	?
Mann, 2012	UK	96	0	53	Breast	Post	Yes	CST	Group	FTF	9	6	Psychologist	UC	SF-36 S	+	+	+	+	+	?

Table 7.1 (continued)

					Intervention									Con.	Quality						
Author (year)	Country	N	Age, mean	Sex (% male)	Diagnosis	Timing	Targeted	Type	Format	Method	Duration	Sessions	Proession		PRO (P or S)	RSG	AC	IO	IR	Adh	Con
Meneses, 2007	USA	261	0	55	Breast	Post	No	CST	Individual	FTF	12	3	Nurse	WLC	QOL-CS P	?	?	+	-	?	?
Northouse, 2005	USA	192	0	54	Breast	During or post	No	CST	Couple	FTF	12	5	Nurse	UC	FACT-G P	+	+	+	+	+	+
Northouse, 2007	USA	263	100	63	Prostate	During or post	No	CST	Couple	FTF	16	5	Nurse	UC	FACT-G P	+	+	+	+	+	+
Northouse, 2013	USA	484	38	60	Advanced lung, col-orectal, breast, and prostate	During or post	No	CST	Couple	FTF	12	3 (brief); 6 (ext.)[a]		UC	FACT-G P	+	+	+	+	+	+
Savard, 2005	CAN	57	0	54	Breast	Post CT and/or RT	Yes	CST	Group	FTF	8	8	Psychologist	WLC	QLQ-C30 P	+	?	+	+	+	?
Savard, 2006	CAN	37	0	51	Meta-static Breast	During or post	Yes	PT	Individual	FTF	8	8	Psychologist	WLC	QLQ-C30 P	+	+	-	+	?	?
van den Berg, 2015	NL	150	0	51	Breast	Post	No	CST	Individual	Web	16	NR	None	UC	QLQ-C30 S	+	+	+	+	+	?

[a] Patients followed a brief (brief) or extended (ext.) intervention.

AC= attention control group; AUS= Australia; CAN= Canada; CST= coping skills training; CT= chemotherapy; FACT-G= Functional Assessment of Cancer Therapy-General; FTF= face-to-face; HT= hormone therapy; NL= the Netherlands; NR= not reported; P= quality of life as primary outcome measure; PRO= patient reported outcome PT= psychotherapy; QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; QOL-CS= cancer-specific quality of life – cancer survivors; RT= radiotherapy; S= quality of life as secondary outcome measure; SF-36= Short Form-36 Item Health Survey; SWE= Sweden; UC= usual care; UK= United Kingdom; USA= United States of America; WLC= wait list control group.

Quality assessment: += high quality; -= low quality; ?= unclear quality; RSG= random sequence generation; AC= allocation concealment; IO= incomplete outcome; IR= incomplete reporting; Adh= adherence; Con= contamination

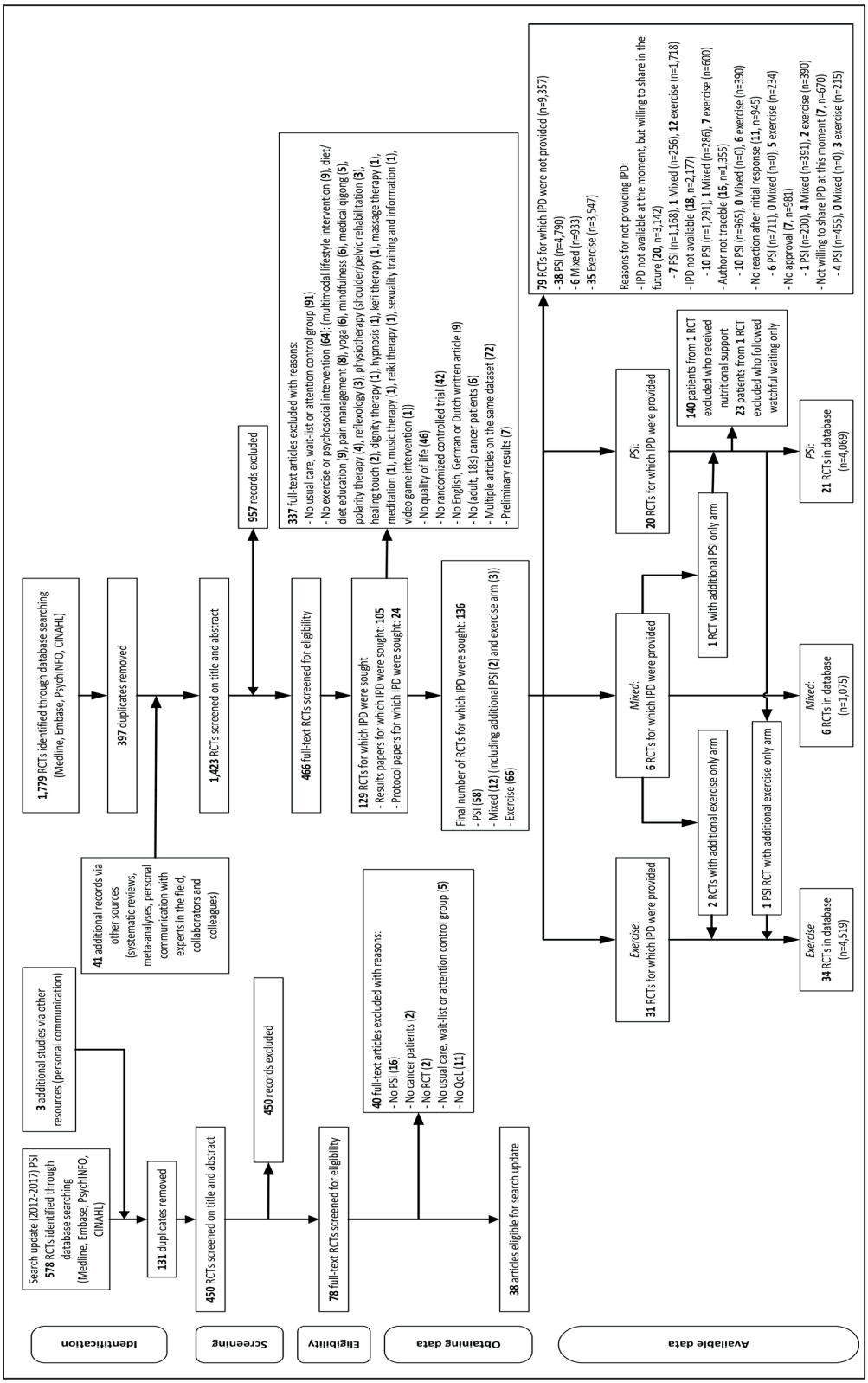


Figure 7.1. Flowchart of study inclusion

IPD= individual patient data; PSI= psychosocial interventions; RCT= randomized controlled trial

and 2,002 to the control group.

In total, 86% of the included RCTs reported random sequence generation, 73% reported adequate allocation concealment, 77% had adequate completeness of outcome data, 82% had complete outcome reporting, 41% described adequate intervention adherence, and 18% provided information on contamination (Table 7.1).

The mean age of participants was 56.0 (standard deviation=11.4) years, 65% were female, 70% were married and/or lived with a partner, 33% were highly educated, 52% were diagnosed with breast cancer, and 9% had a distant metastatic disease at baseline (Table 7.2). Nineteen [37, 39-42, 44-50, 52-57, 59] RCTs evaluated the effects of CST, two [43, 58] evaluated the effects of psychotherapy, and one [51] evaluated information only, 17 were conducted post-cancer treatment, and 8 RCTs targeted patients with distress (Table 7.2).

Representativeness of included studies

The updated search yielded 38 additional RCTs. Of the 99 eligible RCTs, 50 reported summary data on QoL, 47 on EF, and 39 on SF. Of the 22 RCTs included in the IPD meta-analyses, 10 published summary data on QoL, 13 on EF, and 8 on SF. We found no significant differences in effects on QoL (p=0.10), EF (p=0.47), and SF (p=0.66) between RCTs of which IPD were shared (QoL: β= 0.10, 95% CI= -0.03; 0.24, EF: β= 0.13, 95% CI= 0.02; 0.25, SF: β= 0.12, 95% CI= -0.03; 0.27) and those of which IPD were not shared (QoL: β=0.25, 95% CI= 0.14; 0.36, EF: β= 0.19, 95% CI= 0.08; 0.31, SF: β= 0.16, 95% CI= 0.05; 0.27) (Table 7.3).

The Eggers test was not statistically significant for all eligible and RCTs included reporting on QoL, EF, and SF, suggesting no evidence for publication bias.

Table 7.2. Demographic, clinical, personal and intervention-related characteristics, quality of life, emotional function and social function of patients in the intervention and control group

Variable	Intervention (n=2,215)	Control (n=2,002)
Demographic		
Age, mean (SD) years	56.1 (11.5)	56.0 (11.2)
Age categories, n (%)		
<50 years	598 (27.0)	553 (27.6)
50–70 years	1324 (59.8)	1220 (60.9)
≥70 years	292 (13.2)	227 (11.3)
Unknown	1 (0.0)	2 (0.1)
Sex, n (%)		
Male	773 (34.9)	723 (36.1)
Female	1442 (65.1)	1279 (63.9)
Marital status, n (%)		
Single/living alone	555 (25.1)	511 (25.5)
Married/living together	1558 (70.3)	1385 (69.2)
Unknown	102 (4.6)	106 (5.3)
Educational level, n (%)		
Low/medium	1130 (51.0)	1031 (51.5)
High	726 (32.8)	678 (33.9)
Unknown	359 (16.2)	293 (14.6)
Clinical		
Type of cancer, n (%)		
Breast	1153 (52.1)	1039 (51.9)
Genitourinary	625 (28.2)	610 (30.5)
Gynecological	117 (5.3)	106 (5.3)
Gastrointestinal	137 (6.2)	91 (4.5)
Lung	102 (4.6)	61 (3.0)
Hematological	64 (2.9)	76 (3.8)
Other	15 (0.7)	17 (0.8)
Unknown	2 (0.1)	2 (0.1)

Table 7.2 (continued)

Variable	Intervention (n=2,215)	Control (n=2,002)
Distant metastasis at baseline, n (%) [a]		
No	1715 (77.4)	1539 (76.9)
Yes	196 (8.8)	168 (8.4)
Unknown	304 (13.7)	295 (14.7)
Surgery, n (%) [b]		
No	441 (20.1)	351 (18.0)
Prior to intervention	1470 (67.1)	1311 (67.1)
During intervention	75 (3.4)	67 (3.4)
Mid-intervention	167 (7.6)	189 (9.7)
Unknown	38 (1.7)	36 (1.8)
Chemotherapy, n (%)		
No	1058 (47.8)	978 (48.9)
Prior to intervention	579 (26.1)	617 (30.8)
During intervention	526 (23.7)	357 (17.8)
Mid-intervention	4 (0.2)	2 (0.1)
Unknown	48 (2.2)	48 (2.4)
Radiotherapy, n (%)		
No	1023 (46.2)	896 (44.8)
Prior to intervention	647 (29.2)	651 (32.5)
During intervention	324 (14.6)	226 (11.3)
Mid-intervention	154 (7.0)	160 (8.0)
Unknown	67 (3.0)	69 (3.4)
Hormone therapy		
Breast cancer patients (n= 2,192), n (%)		
No	541 (46.9)	445 (42.8)
Yes	522 (45.3)	503 (48.4)
Unknown	90 (7.8)	91 (8.8)
Prostate cancer patients (n= 1,159), n (%)		
No	371 (63.1)	360 (63.0)
Prior to intervention	5 (0.9)	5 (0.9)
During intervention	82 (13.9)	83 (14.5)
Mid-intervention	115 (19.6)	115 (20.1)
Unknown	15 (2.6)	8 (1.4)

Table 7.2 (continued)

Variable	Intervention (n=2,215)	Control (n=2,002)
SCT, n (%) [c]		
Allogenic SCT	0 (0.0)	0 (0.0)
Autologous SCT	24 (37.5)	48 (63.2)
Unknown	40 (62.5)	28 (36.8)
Intervention-related [d]		
Type of intervention, n (%)		
Information only (k=1)	149 (6.7)	
Support (k=0)	0 (0.0)	
Coping skills training (k=19)	1803 (81.4)	
Psychotherapy (k=2)	263 (11.9)	
Timing intervention, n (%) [e]		
Pre and post-treatment (k=1)	372 (16.8)	
During treatment (k=10)	857 (38.7)	
Post-treatment (k=17)	986 (44.5)	
Targeted intervention, n (%)		
No (k=14)	1672 (75.5)	
Yes (k=8)	543 (24.5)	
Format intervention, n (%)		
Individual therapy (k=13)	1287 (58.1)	
Group therapy (k=6)	380 (17.2)	
Couple therapy (k=3)	548 (24.7)	
Method delivery, n (%)		
Face-to-face (k=17)	1671 (75.4)	
Telephone (k=3)	450 (20.3)	
Web-based (k=2)	94 (4.2)	
Profession conducting intervention, n (%)		
Psychologist (k=10)	664 (30.0)	
Nurse (k=7)	1137 (51.3)	
Other (k=5)	414 (18.7)	
Type of control, n (%) [f]		
Usual care (k=14)		1374 (68.6)
Wait list control (k=6)		350 (17.5)
Attention control (k=2)		278 (13.9)

Table 7.2 (continued)

Variable	Intervention (n=2,215)		Control (n=2,002)	
	Pre mean (SD)	Post mean (SD)	Pre mean (SD)	Post mean (SD)
Quality of life, mean (SD) [g]				
FACT-G, total score	74.2 (18.8)	79.3 (16.4)	75.0 (18.1)	77.0 (17.5)
EORTC QLQ-C30, subscale global QoL	65.8 (20.6)	71.3 (20.6)	66.4 (20.1)	69.4 (18.8)
QoL-CS, total score	6.8 (1.4)	7.2 (1.3)	6.8 (1.5)	6.9 (1.5)
SF-36, subscale general health	69.0 (19.3)	70.6 (19.0)	69.6 (19.2)	70.1 (20.0)
Emotional function, mean (SD) [g]				
FACT-G, subscale EWB	15.7 (4.9)	17.4 (4.4)	15.7 (4.6)	16.6 (4.2)
EORTC QLQ-C30, subscale EF	73.6 (22.0)	80.2 (20.1)	74.1 (21.5)	78.0 (20.9)
QoL-CS, subscale PWB	5.9 (1.7)	6.3 (1.6)	6.2 (1.7)	6.1 (1.8)
SF-36, subscale EF	80.7 (29.2)	81.4 (27.8)	83.5 (27.7)	81.0 (27.6)
Social function, mean (SD) [g]				
FACT-G, subscale SWB	20.2 (6.2)	21.2 (5.6)	19.9 (5.9)	19.6 (6.1)
EORTC QLQ-C30, subscale SF	77.6 (25.0)	83.9 (22.4)	76.5 (25.8)	82.5 (22.8)
QoL-CS, subscale SWB	6.4 (1.7)	7.1 (1.9)	6.6 (1.8)	7.0 (1.9)
SF-36, subscale SF	82.2 (22.7)	80.1 (23.2)	85.0 (20.7)	80.1 (23.3)

EF= emotional function; EORTC QLQ-C30= European Organisation Research and Treatment of Cancer Quality of life questionnaire-Core 30; EWB= emotional well-being; FACT-G= Functional Assessment of Cancer Therapy-General; k= number of trials; n= number of patients; PWB= psychological well-being; QoL-CS= quality of life-cancer survivors; SF-36= Short Form-36 Health survey; SCT= stem cell transplantation; SD= standard deviation; SF= social function; SWB= social well-being.

[a] proportion of patients of solid tumours (n=4,145); [b] proportion of patients without SCT (n=4,145); [c] proportion of patients with SCT (n=72); [d] proportion of patients from intervention groups (n=2,215); [e] some trials included patients during and post-treatment (k=6) and therefore the total number of trials exceeds 22; [f] proportion of patients from the control groups (n=2,002). [g] Higher scores represents higher QoL for FACT-G, EORTC QLQ-C30, QoL-CS, and SF-36

Effects and moderators of PSI on QoL EF and SF

PSI significantly improved QoL (β= 0.14, 95% CI= 0.06; 0.21), EF (β= 0.13, 95% CI= 0.05; 0.20), and SF (β= 0.10, 95% CI= 0.03; 0.18), see Table 7.4 and Figure 7.2. Intervention effects on QoL (p=0.05), EF (p<0.01), and SF (p=0.05) were

Table 7.3. Representativeness and publication bias of the pooled effects of studies providing data for the POLARIS study and those not providing data

		Pooled effect	Test of heterogeneity			Between group difference
Representativeness	**k**	**g (95% CI)**	**Q**	**I^2**	**p-value**	**p-value**
Quality of life						
All eligible RCTs	50	0.21 (0.12; 0.30)*	133.27	60.23	<0.01	
RCTs providing data	10	0.10 (-0.03; 0.24)	16.92	40.91	0.08	
RCTs not providing data	40	0.25 (0.14; 0.36)*	112.34	62.61	<0.01	0.10
Emotional function						
All eligible RCTs	47	0.17 (0.09; 0.26)*	135.21	61.54	<0.01	
RCTs providing data	13	0.13 (0.02; 0.25)*	25.79	45.71	0.03	
RCTs not providing data	34	0.19 (0.08; 0.31)*	107.62	65.62	<0.01	0.47
Social function						
All eligible RCTs	39	0.14 (0.06; 0.23)*	75.04	46.69	<0.01	
RCTs providing data	8	0.12 (-0.03; 0.26)	14.29	37.00	0.11	
RCTs not providing data	31	0.16 (0.05; 0.27)*	60.65	50.53	<0.01	0.66
Publication bias using trim and fill procedure	**$k_{missing}$**	**Adjusted effect**			**P_{Egger} [a]**	
Quality of life						
All eligible RCTs	0	0.21 (0.12; 0.30)*			0.21	
RCTs providing data	0	0.10 (-0.03; 0.24)			0.64	
Emotional function						
All eligible RCTs	0	0.17 (0.09; 0.26)*			0.42	
RCTs providing data	0	0.13 (0.02; 0.24)*			0.69	
Social function						
All eligible RCTs	6	0.21 (0.11; 0.30)*			0.25	
RCTs providing data	2	0.17 (0.01; 0.33)*			0.07	

[a] The Egger's test investigates the publication bias captured by the funnel plot

k= number of trials; RCTs= randomized controlled trials; CI= confidence interval. *p<0.05

Table 7.4. Effects and moderators of psychosocial interventions on quality of life, emotional function, and social function. Regression coefficients (β) and 95% confidence intervals (CI) of the intervention effects, and p-value of the likelihood ratio test of models with and without interactions are presented

	QoL		Emotional function		Social function	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Effect of psychosocial interventions	0.14 (0.06; 0.21)*		0.13 (0.05; 0.20)*		0.10 (0.03; 0.18)*	
Age, years		0.05		<0.01		0.05
<50 years	0.25 (0.15; 0.36)*		0.22 (0.11; 0.33)*		0.24 (0.14; 0.34)*	
50–70 years	0.08 (0.01; 0.14)*		0.11 (0.05; 0.17)*		0.06 (-0.00; 0.12)	
≥70 years	0.07 (-0.06; 0.20)		-0.01 (-0.14; 0.12)		0.03 (-0.10; 0.15)	
Sex (men vs women)		0.15		0.85		0.87
Marital status		0.55		0.03		0.88
Single/ living alone	…		0.29 (0.18; 0.40)*		…	
Married/ living with partner	…		0.09 (0.03; 0.15)*		…	
Education level (low-medium vs high)		0.41		0.66		0.40
Type of cancer		0.35		0.02		0.89
Breast	…		0.15 (0.08; 0.23)*		…	
Genitourinary	…		0.07 (-0.00; 0.15)		…	
Hematological	…		0.14 (-0.11; 0.38)		…	
Gastrointestinal	…		-0.10 (-0.36; 0.16)		…	
Gynecological	…		0.27 (-0.06; 0.60)		…	
Lung	…		0.23 (-0.06; 0.51)		…	
Other	…		-0.66 (-1.47; 0.16)		…	
Type of cancer (breast vs other)		0.19		0.97		0.59
Distant metastasis at baseline		0.64		0.60		0.60
Surgery		0.81		0.40		0.08

Table 7.4 (continued)

	QoL		Emotional function		Social function	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Chemotherapy		0.01		0.03		0.14
No	0.03 (-0.04;0.10)		0.06 (-0.01; 0.12)		…	
Yes	0.22 (0.15;0.29)*		0.20 (0.12; 0.27)*		…	
Radiotherapy		0.80		0.05		0.09
No	…		0.16 (0.08; 0.23)*		…	
Yes	…		0.09 (0.02; 0.16)*		…	
Hormone therapy for breast cancer		0.88		0.61		0.06
Hormone therapy for prostate cancer		0.75		0.17		0.66
Baseline value of outcome [a]		0.40		0.02		0.14
< -0.5 SD	…		0.17 (0.05; 0.29)*		…	
-0.5 to 0.5 SD	…		0.14 (0.06; 0.23)*		…	
> 0.5 SD	…		0.08 (0.01; 0.15)*		…	
Type of intervention		0.01		0.01		< 0.01
Providing information	0.19 (0.03; 0.34)*		0.11 (-0.06; 0.28)		0.06(-0.09;0.22)	
Support	-		-		-	
CST	0.09 (0.04; 0.15)*		0.10 (0.04; 0.15)*		0.08 (0.03; 0.13)*	
Psychotherapy	0.32 (0.12; 0.51)*		0.31 (0.10; 0.53)*		0.38 (0.16; 0.61)*	
Timing of intervention delivery (during vs post-treatment)		0.81		0.31		0.69

Table 7.4 (continued)

	QoL		Emotional function		Social function	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Targeted intervention		< 0.01		0.01		<0.01
No	0.07 (0.02; 0.12)*		0.09 (0.04; 0.14)*		0.06 (0.01; 0.11)*	
Yes	0.32 (0.20; 0.43)*		0.21 (0.06; 0.35)*		0.26 (0.14; 0.38)*	
Intervention duration (≤ 12 week vs > 12 weeks)		0.14		0.27		0.26

SD= standard deviation

[a] baseline QoL as moderator for outcome QoL, baseline emotional function as moderator for outcome emotional function, baseline social function as moderator for outcome social function

* p<0.05

significantly larger for younger patients. Intervention effects on EF (p=0.03) were larger for patients who were single and/or living alone (β= 0.29, 95% CI= 0.18; 0.40) compared to married and/or living with partner (β= 0.09, 95% CI= 0.03; 0.15). Effects on EF differed by cancer type (p=0.02). Effects on QoL (p=0.01) and EF (p=0.03) were larger for patients who were treated with chemotherapy. Intervention effects on EF were significantly larger for patients who did not receive radiotherapy (p=0.05). Intervention effects on EF (p=0.02) were larger for patients with lower EF at baseline. Type of PSI (p≤0.01) significantly moderated the effects on QoL, EF and SF, with largest effects for psychotherapy (QoL: β= 0.32, 95% CI= 0.12; 0.51, EF: β= 0.31, 95% CI= 0.10; 0.53, SF: β= 0.38, 95% CI= 0.16; 0.61). Intervention effects on QoL (p<0.01), EF (p=0.01), and SF (p<0.01) were significantly larger in studies that specifically targeted patients with distress.

Figure 7.2. Forest plots of the effects of psychosocial intervetions on quality of life (a), emotional function (b), and social function (c)

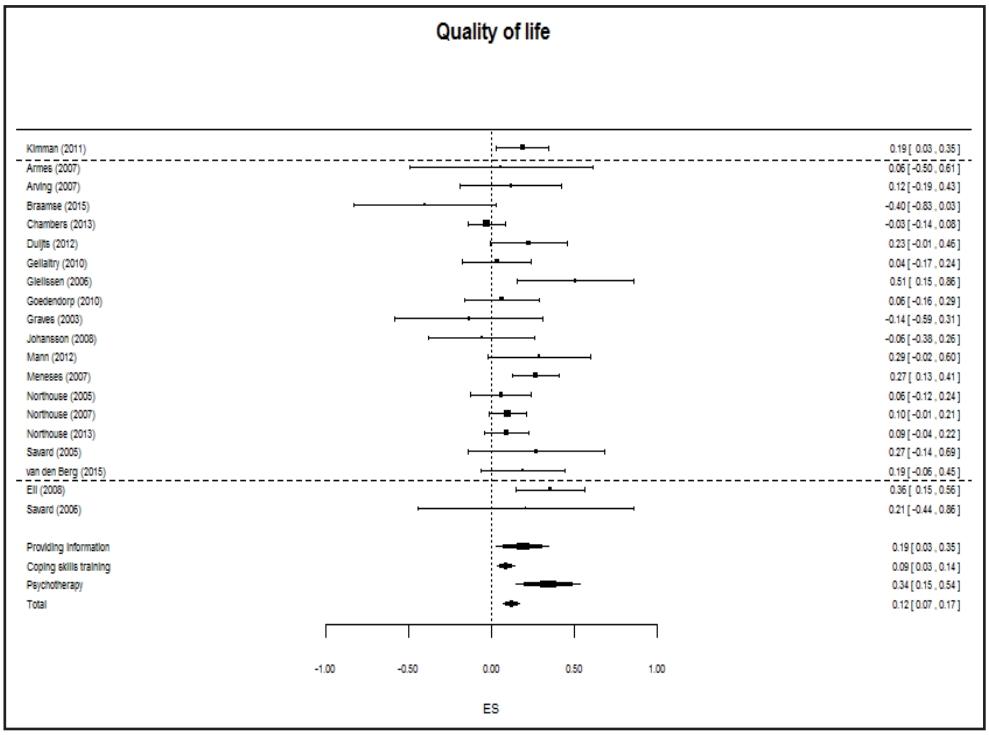
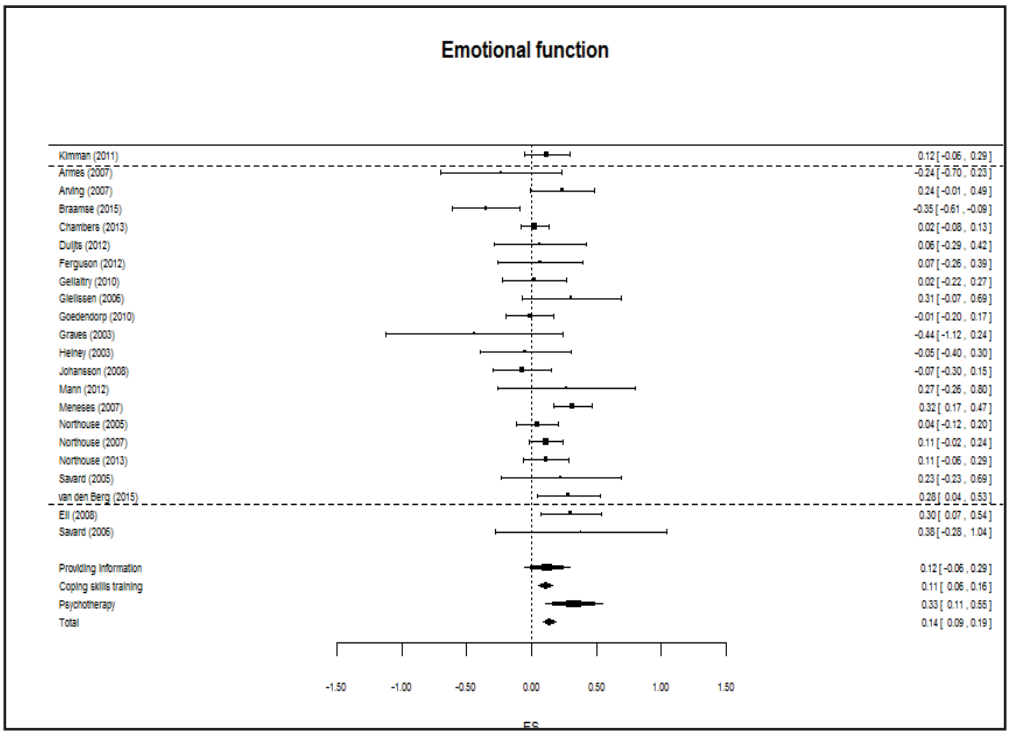


Figure 7.2 (continued)



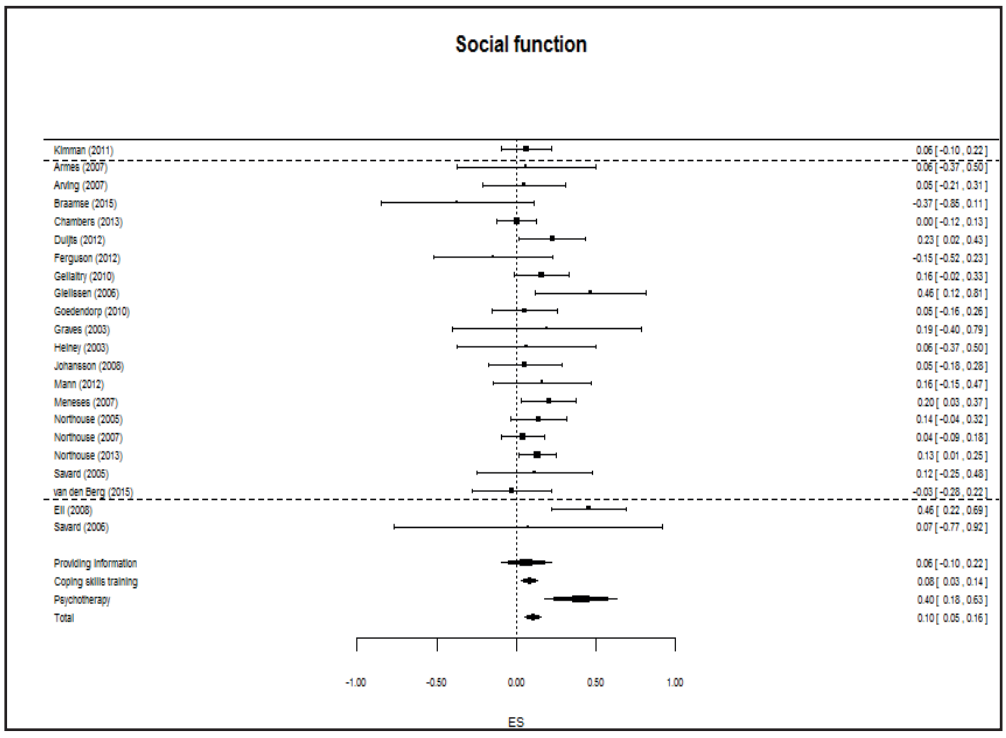


Table 7.5. Effects and moderators of coping skills training (CST) on quality of life, emotional function, and social function. Regression coefficients (β) and 95% confidence intervals (CI) of the intervention effects, and p-value of the likelihood ratio test of models with and without interactions are presented

	QoL		Emotional function		Social function	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Effect of CST interventions	0.11 (0.03; 0.20)*		0.10 (0.02; 0.18)*		0.09 (0.04; 0.15)*	
Age, years		0.11		0.01		0.03
<50 years	…		0.19 (0.07; 0.32)*		0.24 (0.12; 0.36)*	
50–70 years	…		0.09 (0.02; 0.16)*		0.04 (-0.03; 0.11)	
≥70 years	…		-0.02 (-0.16; 0.11)		0.03 (-0.11; 0.17)	
Sex (men vs women)		0.08		0.77		0.84
Marital status (single/living alone vs married/living with partner)		0.33		0.06		0.68
Education level (low-medium vs high)		0.74		0.79		0.57
Type of cancer		0.81		0.56		0.27
Type of cancer (breast vs other)		0.39		0.63		0.40
Distant metastasis at baseline		0.58		0.61		0.47
Surgery		0.75		0.53		0.04
No	…		…		-0.03 (-0.15; 0.09)	
Yes	…		…		0.14 (0.07; 0.20)*	
Chemotherapy		0.01		0.01		0.08
No	0.01 (-0.06; 0.08)		0.03 (-0.04; 0.10)		…	
Yes	0.21 (0.13; 0.29)*		0.18 (0.09; 0.27)*		…	
Radiotherapy		0.89		0.24		0.19

Table 7.5 (continued)

	QoL		Emotional function		Social function	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Hormone therapy for breast cancer		0.59		0.42		0.01
No	…		…		0.23 (0.12; 0.35)*	
Yes	…		…		0.05 (-0.05; 0.15)	
Hormone therapy for prostate cancer		0.85		0.17		0.63
Baseline value of outcome [a]		0.83		0.14		0.13
Timing of intervention delivery (during vs post-treatment)		0.36		0.76		0.35
Targeted intervention		< 0.01		0.34		0.18
No	0.06 (0.00; 0.12)*		…		…	
Yes	0.30 (0.16; 0.45)*		…		…	
Intervention duration (≤12 week vs >12 weeks)		0.16		0.27		0.26

SD= standard deviation

[a] baseline QoL as moderator for outcome QoL, baseline emotional function as moderator for outcome emotional function, baseline social function as moderator for outcome social function

* p<0.05

Stratified analyses per intervention type

Effects and moderators of coping skills training (19 RCTs)

CST significantly improved QoL (β= 0.11, 95% CI= 0.03; 0.20), EF (β= 0.10, 95% CI= 0.02; 0.18), and SF (β= 0.09, 95% CI= 0.04; 0.15), see Table 7.5. Patients who were younger had larger effects of CST on EF (p=0.01) and SF (p=0.03). Patients treated with chemotherapy had larger CST effects on QoL and EF (p=0.01). Patients treated with surgery had larger effects on SF (p=0.04). Effects on SF was also larger in women with breast cancer who did not receive hormone therapy (p=0.01). Effects on QoL (p<0.01) were larger in studies that targeted patients with distress. Sensitivity analyses among patients with breast cancer (n=1,753) showed larger CST effects on EF (p=0.03) in patients treated with chemotherapy.

Effects and moderators of psychotherapy (2 RCTs)

Psychotherapy significantly improved QoL (β= 0.45, 95% CI= 0.15; 0.75), EF (β= 0.36, 95% CI= 0.06; 0.66), and SF (β= 0.34, 95% CI= 0.07; 0.62), see Table 7.6. Type of cancer moderated the intervention effects of psychotherapy on EF (p=0.02). Intervention effects on EF were significant for patients with breast (β= 0.46, 95% CI= 0.06; 0.87), and hematological cancer (β= 1.11, 95% CI= 0.34; 1.87).

Discussion

This IPD meta-analysis of 22 RCTs, including 4,217 patients with cancer, showed that PSI significantly improved QoL, EF and SF, with small overall effects, both during and after treatment. The present IPD meta-analysis enabled the testing of potential moderators of intervention effects using interaction tests in a large sample. In the current sample, of which half of the population was diagnosed with breast cancer and one third with genitourinary cancer, we found significant differences in effects of different types of PSI, with largest effects of psychotherapy in comparison with CST and providing information. The effects of CST were moderated by age, treatment type, and by targeted interventions. The effects of psychotherapy on EF may be moderated by cancer type, but these analyses were based on two RCTs with small

Table 7.6. Effects and moderators of psychotherapy interventions on quality of life, emotional function, and social function. Regression coefficients (β) and 95% confidence intervals (CI) of the intervention effects, and p-value of the likelihood ratio test of models with and without interactions are presented

	QoL		Emotional function		Social function	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Effect of psychotherapy	0.45 (0.15; 0.75)*		0.36 (0.06; 0.66)*		0.34 (0.07; 0.62)*	
Age, years		0.50		0.22		0.58
Sex (men vs women)		0.54		0.62		0.34
Marital status (single/living alone vs married/living with partner)		0.68		0.25		0.56
Education level (low-medium vs high)		0.22		0.14		0.74
Type of cancer		0.07		0.02		0.38
Breast	...		0.46 (0.06; 0.87)*		...	
Genitourinary	...		0.49 (-0.04; 1.03)		...	
Hematological	...		1.11 (0.34; 1.87)*		...	
Gastrointestinal	...		-0.70 (-1.65; 0.24)		...	
Gynecological	...		0.36 (-0.02; 0.75)		...	
Lung	...		-		...	
Other	...		-0.86 (-2.72; 1.01)		...	
Type of cancer (breast vs other)		0.22		0.49		1.00
Surgery		0.31		0.23		0.19
Chemotherapy		0.64		0.66		0.30
Radiotherapy		0.08		0.09		0.09
Hormone therapy for breast cancer		0.51		0.38		0.78
Baseline value of outcome [a]		0.74		0.20		0.49
Timing of intervention delivery (during vs post-treatment)		0.31		0.23		0.24

SD= standard deviation. [a] baseline QoL as moderator for outcome QoL, baseline emotional function as moderator for outcome emotional function, baseline social function as moderator for outcome social function. * p<0.05.

sample sizes of some cancer types.

Our finding that the effects on QoL, EF, and SF were larger for psychotherapy than for CST differs from a previous summary data meta-analysis that summarized the results of 37 RCTs in a mixed cancer population and reported no difference in effects between information provision (6 RCTs), support (4 RCTs), CST (20 RCTs), and psychotherapy (7 RCTs) [12]. However, our finding should be interpreted with caution, since we were only able to include two RCTs evaluating psychotherapy interventions, and they were offered to patients with mixed cancer types [43] or metastatic breast cancer [58]. These two RCTs also targeted patients with higher levels of depressive symptoms, which may explain the larger effects of psychotherapy compared to CST [60].

The larger effects of CST in younger patients found in the current IPD meta-analysis may be explained by the higher psychological distress and supportive care needs of younger patients in physical, informational, and emotional domains [61, 62]. Consequently, CST may more effectively improve EF and SF for this subgroup of patients. Alternatively, older patients with cancer may have specific needs that were not, or only partly, addressed by CST [61]. There is limited knowledge, however, about the supportive care needs of elderly patients with cancer, who more often have comorbid conditions [61]. Further research is needed to identify the supportive care needs of elderly patients with cancer and to develop effective CST targeting this population.

Treatment type was a significant moderator effect of CST, such that larger effects on QoL and EF were found in patients treated with chemotherapy, and effects on SF were larger in patients with breast cancer that did not receive hormone therapy, and in patients who had surgery. The larger effects of CST in patients treated with chemotherapy compared to those who were not may be explained by the specific side effects of chemotherapy, including fatigue [63], pain [64], and emotional or cognitive problems [65], which are specifically targeted by CST. The larger effects in patients who did not receive hormone therapy may also be caused by milder side effects of hormone therapy, compared to chemotherapy. Additionally, patients with hormone sensitive tumors have generally have a lower risk of disease recurrence than patients with hormone insensitive tumors [66]. The larger effects of CST on SF

in patients who had surgery, should be interpreted with caution as this may vary by type of surgery (e.g. radical mastectomy versus breast-preserving surgery [67]). Additionally, we used broad categories of treatment in this heterogeneous group of patients and treatment combinations and intervention timing may vary. Future studies should therefore examine moderator effects of cancer treatment within more homogeneous groups of patients. Our sensitivity analyses in women with breast cancer showed larger CST effects on EF in those treated with chemotherapy, emphasizing that CST is particularly beneficial in women with breast cancer treated with chemotherapy.

We observed a larger effect of CST on QoL in RCTs that specifically targeted patients with higher levels of distress before the intervention. This underlines the importance of targeting patients with distress so that the limited available resources for CST can be targeted to those who need and benefit most from CST. Unexpectedly, despite larger effects in targeted studies, no moderator effect of the baseline value of QoL, EF and SF was found. Also previous studies on the moderator effect of baseline distress were inconsistent [1, 5, 18, 60, 68].

In the two RCTs that studied the effects of psychotherapy, that specifically targeted patients with distress, we found a significant moderator effect of cancer type. Effects on EF were significant for patients with breast and hematological cancer. Due to the small sample size of some cancer types, future studies should confirm whether patients with different cancer types indeed respond differently to interventions.

Strengths and limitations

Strengths of this study include the IPD approach and the large number of RCTs from multiple countries and the resulting large sample size that enabled testing of interactions between the intervention and patient-level characteristics and conducting subsequent stratified analyses, as well as the uniform analytical procedures across all studies. The study also had a number of limitations that should be noted. First, the pooled RCTs were heterogeneous with respect to type of intervention and cancer. Future studies with more homogeneous patient samples are needed to investigate potential moderator effects of PSI-related characteristics

and techniques such as delivery format (e.g. individual, group or couple therapy), method (e.g. face-to-face, telephone, or web-based), and profession (e.g. psychologist versus nurse). Also, other potential psychosocial moderators of PSI effects such as coping skills, self-esteem and perceived social support were not explored [19, 69], and should therefore be examined in future studies. Another limitation is the time between the literature search and the current publication. The collection of IPD from multiple RCTs is very time consuming, and it took more than three years to collect these data, which is comparable to IPD meta-analysis in other fields of research [22]. In addition, during these three years, we maintained contact with PI's of ongoing studies (n=6) of which protocol papers were identified, and these were included in the current IPD meta-analysis. The results of the moderator analyses, however, are novel and valid. Third, only 36% of the eligible RCTs were included in the IPD meta-analysis, which may limit the generalizability of the results [70]. However, we found no differences in effect sizes between RCTs included and those not included, indicating that the 22 RCTs included in the analyses were a representative sample of the published studies. Additionally, the results of the current analyses depend on the studies conducted so far, thus mainly among patients with breast and genitourinary cancer, and may therefore not be generalizable to other cancer populations. Fourth, some biases were present in the included RCTs, with little information on adherence to the PSI and potential contamination in the control group. Adherence and contamination may influence the intervention effect as well. With study quality being a study-level characteristic of which the power is determined by the number of studies, it is difficult to disentangle the impact of study quality versus other intervention-related characteristics and techniques on the moderator effects. Therefore the quality rating was added to inform the reader about the overall study quality. Finally, as 11 of the 22 RCTs did not provide sufficient data at follow-up or used different follow-up durations, we were not able to study the intervention effects at long-terms.

Clinical implications

Our study showed that PSI significantly improves QoL, EF, and SF both during and post cancer treatment, but the overall effects are small. Psychotherapy appears to have larger effects compared to CST, but this conclusion is based on just two

psychotherapy interventions that specifically targeted patients with distress. The effects of existing CST were larger for interventions that were targeted, and in patients who were younger. Additionally, treatment type moderated the effects of CST. CST was particularly beneficial in patients treated with chemotherapy. Our study highlights the importance of targeted interventions, and it presents the need of developing interventions tailored to the specific needs of elderly patients.

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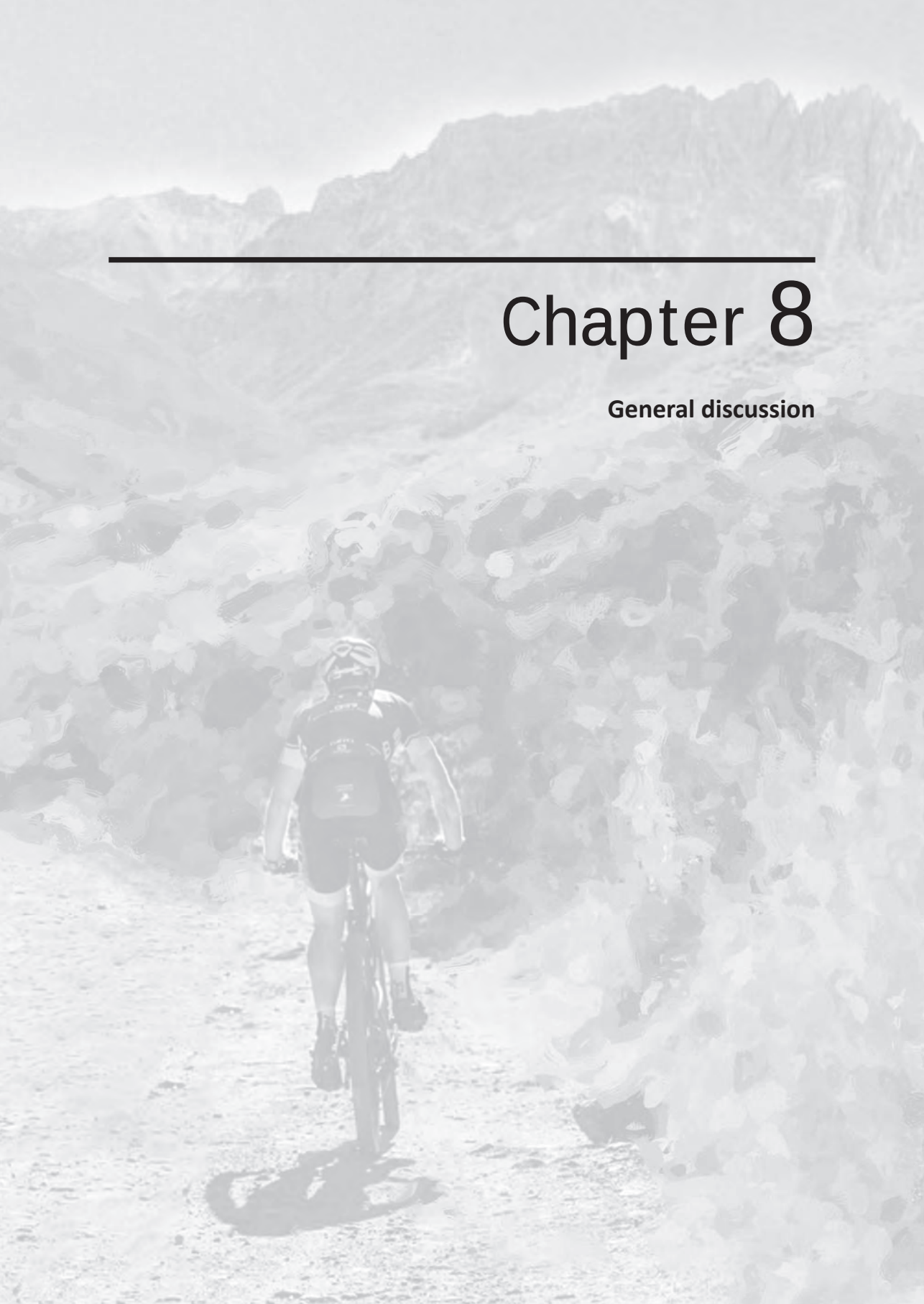

Chapter 8

General discussion

Current exercise and psychosocial interventions are typically offered to a heterogeneous group of patients with cancer and are not targeted to specific patients. Such a 'one-size-fits all' approach may explain the modest effects of these interventions that have been reported. Therefore, these interventions should be better targeted and tailored to specific characteristics of patients. To be able to shift from this 'one-size-fits-all' approach to more personalized exercise and psychosocial interventions, it is important to identify which subgroups of patients respond best to these interventions. Furthermore, to improve the effectiveness of exercise and psychosocial interventions on quality of life (QoL) among patients with cancer, insights into the working mechanisms of an intervention are needed. Therefore, this thesis aimed to investigate the effects of exercise and psychosocial interventions on QoL in patients with cancer during and after cancer treatment, and to identify demographic, clinical, personal and intervention-related moderators of these intervention effects. Further, this thesis investigated some possible mechanisms underlying the effects of exercise interventions on QoL. Finally, this thesis aimed to build a flexible data harmonization platform that facilitates harmonizing raw individual patient data (IPD) of original studies for meta-analyses purposes, where such harmonization already starts during collection of the data from the original studies. The Predicting OptimaL Cancer RehabIlitation and Supportive care (POLARIS) study used this platform. POLARIS included IPD from 57 randomized controlled trials (RCTs) that evaluated the effects of exercise interventions and/or psychosocial interventions on QoL compared to a wait-list, usual care or attention control group in adult patients with cancer. After briefly summarizing and discussing the main findings of this thesis, the methodological considerations are discussed. This is followed by implications for clinical practice, recommendations for future research, and a general conclusion.

Main findings

Effects and moderators of exercise and psychosocial interventions on QoL in patients with cancer

The first aim of this thesis was to investigate the effects of exercise and psychosocial interventions on QoL in patients with cancer during and after treatment, and to identify moderators of these intervention effects.

The single study described in Chapter 2 suggests that the effects of a group-based exercise intervention on global QoL in patients after cancer treatment were larger for patients who received radiotherapy, and in particular, in those who received a combination of chemotherapy and radiotherapy, and in patients with higher levels of fatigue at baseline (i.e. prior to the exercise intervention). No moderator effects were found for age, sex, education level, marital status, employment status, time since treatment, presence of comorbidity, self-efficacy, depression, and anxiety. This study was a first step in identifying patients who may benefit most from exercise interventions to improve QoL [1]. However, single studies are generally not powered to analyze moderators of intervention effects and to conduct subsequent stratified analysis [1]. Therefore, the POLARIS study was launched allowing to set up and conduct meta-analyses of IPD.

Results of the POLARIS IPD meta-analysis of 34 RCTs (n=4,519 patients) evaluating the effects and demographic, clinical, intervention- and exercise-related moderators of exercise on QoL and physical function in patients with cancer, demonstrated that exercise interventions significantly improved QoL and physical function, with small overall effects (Chapter 6). These findings are consistent with those reported in previous meta-analyses based on aggregate data [2-4]. Furthermore, the results presented in this thesis showed that the effects of exercise interventions in which (part of) the weekly exercise sessions were supervised, were twice as large as those of exercise interventions in which sessions were unsupervised and conducted at or from home. No significant moderator effects were found for age, sex, education level, marital status, body mass index, cancer type, the presence of distant metastasis, and type of cancer treatment. Besides, exercise interventions during and after cancer treatment were found to be equally beneficial for QoL and physical function. Results of earlier RCTs that evaluated whether or not demographic and clinical characteristics moderated the exercise intervention effects on QoL and physical function were inconsistent [5-9]. Findings from this thesis suggests that targeting exercise interventions based on these demographic and clinical characteristics may not be useful for further improving QoL and physical function.

Results of the POLARIS IPD meta-analysis on 22 RCTs with a total sample size of 4,217 patients, that investigated the effects of psychosocial interventions on QoL showed that these interventions have statistically significant but small beneficial effects on QoL, emotional function, and social function, both during and after

treatment (Chapter 7). This is consistent with results from previous meta-analyses in this field that used aggregate data [10-22]. Psychotherapy appeared to have larger effects compared to coping skills training and providing information, but this conclusion was based on two psychotherapy intervention studies that investigated interventions that specifically targeted patients with psychological distress. The effects of coping skills training were moderated by age, treatment type, and targeted interventions (i.e. targeted to patients with distress). The effects of coping skills training on emotional and social function were larger among younger patients, which may be explained by the higher psychological distress and supportive care needs of younger patients in physical, informational, and emotional domains [23, 24]. Consequently, coping skills training may be more effective to improve emotional function and social function for this subgroup of patients. However, effects of coping skills training on emotional function and social function were not moderated by baseline values of emotional and social function. Further, type of cancer treatment was a significant moderator of the effect of coping skills training, such that larger effects on QoL and emotional function were found in patients treated with chemotherapy, and larger effects on social function were found in patients with breast cancer that did not receive hormone therapy, and in patients who had surgery. The larger effects of coping skills training in patients treated with chemotherapy may be explained by the systemic effect of chemotherapy, that may lead to an increased level of symptoms such as fatigue [25], and emotional or cognitive problems [26], which are specifically targeted by coping skills training. It should be noted, however, that broad categories of treatments were used in this heterogeneous group of patients (i.e. previous or current treatment versus no such treatment) and treatment combinations may vary. Future studies should therefore examine moderator effects of cancer treatment within more homogeneous groups of patients. Furthermore, effects of coping skills training on QoL were larger in studies that targeted patients with distress. It is known that higher levels of distress negatively affect a patient's QoL [27]. Coping skills training may reduce distress and consequently improve a patient's QoL [10]. Patients with higher levels of distress at baseline may have more room for reducing their distress, and consequently have larger improvements in QoL. However, effects of coping skills training on QoL was not moderated by baseline values of QoL. The effects of psychotherapy on emotional function seems to be moderated by cancer type, with significantly higher effects for patients with breast and hematological cancer compared to other

cancer types. However, it may be that the moderating effect of cancer type on the psychotherapy effects on QoL was coincidental due to the small sample size of some other cancer types included in the analyses. Therefore, future studies are needed to confirm whether patients with different cancer types indeed respond differently to psychosocial interventions. Overall, this IPD meta-analysis stresses the need for developing a coping skills training tailored to the specific needs of elderly patients, and it highlights the importance of targeting psychosocial interventions to patients with distress.

Mechanisms underlying exercise intervention effects on QoL

The second aim of this thesis was to investigate the mechanisms underlying the effects of exercise interventions on QoL.

The study described in Chapter 3 found support for the hypothesis that a 12-week resistance and endurance exercise intervention improved cardiorespiratory fitness, which is associated with lower physical fatigue and higher global QoL and physical function. The mediating role of cardiorespiratory fitness in the exercise intervention effect on physical fatigue and physical function emphasizes the importance of improving cardiorespiratory fitness in patients with cancer. The lack of a mediating effect of improved cardiorespiratory fitness on general fatigue is in line with previous studies [28, 29]. This may be explained by the fact that general fatigue does not only include physical aspects, but also mental aspects, which are likely to be influenced by concepts other than or additional to cardiorespiratory fitness. Furthermore, higher handgrip strength was associated with lower physical fatigue, and better lower body muscle function was associated with lower general and physical fatigue, which indicate that muscle strength and function might be important intervention targets when aiming to reduce fatigue. However, muscle strength and function did not mediate the exercise effects on fatigue and physical function, because no significant effect of the exercise intervention was found on this outcome. The lack of significant effects of exercise on muscle strength and function may be related to the choice of instruments used to assess the outcomes, as they may have been less sensitive to detect exercise-induced changes [9]. Finally, reducing fatigue was associated with improved global QoL and physical function, and exercise appeared to be an effective strategy to reduce fatigue.

Research into the mechanisms underlying psychosocial intervention effects on QoL were beyond the scope of the current thesis. However, data collected in the POLARIS study will allow to explore which factors may mediate the effect of psychosocial interventions on QoL.

A flexible data harmonization platform that facilitates harmonizing data during data collection

The third aim of this thesis was to build a flexible data harmonization platform for use in IPD meta-analyses that facilitates harmonization of IPD already during the process of data collection. Chapter 5 describes the development and use of this platform. This platform is the first data harmonization platform that allows starting data harmonization already during data collection, which is time efficient, especially when the number of studies is large. Furthermore, the data harmonization platform allows to store, prepare, and harmonize IPD within one transparent platform. The harmonization process is facilitated by transparent interfaces, which makes the platform easy in use. Finally, the data harmonization platform has the ability to export harmonized IPD and corresponding data dictionary to the statistical program SPSS [30] for further analysis.

Methodological considerations

When interpreting the main findings of this thesis, it is important to take into account methodological considerations related to statistical power, study design, primary outcome, potential sources of bias in IPD meta-analyses, and generalizability. These considerations are discussed below.

Statistical power

In Chapter 2, possible moderators of exercise intervention effects on QoL were studied in a single study that evaluated the effects of a 12-week group-based exercise program among patients with cancer who completed cancer treatment. Although the sample size of this study was relatively large for an exercise trial in patients with

cancer (n= 209), the sample size was small for studying intervention moderators. In fact, the results of the presented power analyses showed that the sample size should be at least 395 to be able to adequately conduct stratified analyses with a power of 80%. Consequently, the analyses of the moderator effects described in this study should be interpreted as exploratory (hypothesis generating) analyses [1]. To confirm findings from single studies or to identify new intervention moderators, a meta-analysis using IPD has been suggested as the preferred method [31, 32]. The large number of raw data points in an IPD meta-analysis facilitates testing of interactions at the patient level, conducting subsequent stratified analyses, and standardizing analytic techniques across the included studies [31, 32]. With over 4,500 patients included in the IPD meta-analyses that studied the moderators of exercise on QoL and physical function (Chapter 6) and over 4,200 patients included in the IPD meta-analyses that studied moderators of psychosocial intervention on QoL, emotional function and social function (Chapter 7), there was sufficient power to test potential moderators of intervention effects, and conduct subsequent stratified analyses accordingly. To the best of our knowledge, the POLARIS study is currently the largest IPD meta-analysis study in this field of research. However, the search was conducted in September 2012, and, despite maintaining contact with principal investigators of identified ongoing trials, not all relevant studies published since September 2012 were included in the POLARIS database as used in the present thesis.

Study design

In Chapter 4, possible physical and psychological mediators of exercise intervention effects on QoL were studied in a single RCT that evaluated the effects of a combined resistance and endurance exercise intervention among patients with cancer who had completed treatment with curative intent [9, 33]. Although a RCT with pre- and post-intervention measurements is considered the most rigorous study design to evaluate the effectiveness of an intervention [34], the disadvantage of using this design for mediation analysis is that inferences about causality between mediators and outcome variables cannot be made because the mediator variables and outcome variables were assessed at the same time-points. Preferably, a longitudinal design with multiple assessment points is needed where the exercise-induced changes in

the mediator can precede the changes in the outcome QoL [5].

On the contrary, RCTs with pre-and post-intervention measurements are suitable for studying possible moderators of intervention effects. The use of meta-analyses in which IPD of multiple RCTs are pooled (as used for the studies presented in Chapter 6 and 7) is the best way to study whether the effects of an intervention differ across subgroups of patients, as the large sample sizes provide sufficient statistical power to detect moderators of intervention effects and conduct subsequent stratified analyses [31, 32].

Primary outcome

The primary outcome of the studies in this thesis was QoL, which is typically assessed with patient-reported outcomes (e.g. cancer-specific QoL questionnaires such as the Functional Assessment of Cancer Therapy [35] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 questionnaire [36], and the generic QoL questionnaire Short Form-36 [37]). Although these questionnaires are well-known, widely used, reliable and valid instruments to measure QoL [35-37], they have limitations. QoL may, for instance, be susceptible to 'response shift', i.e. a recalibration of a participant's internal standard used to judge one's current QoL experience [38, 39]. This internal standard of QoL perception may change throughout the cancer continuum [40]. Therefore, 'response shift' should be taken into account when evaluating the exercise and psychosocial intervention effect on QoL in a longitudinal study design.

Potential sources of bias in IPD meta-analyses

Despite advantages of IPD meta-analyses, such as the ability to use consistent statistical methods across studies, obtain results for unpublished or poorly reported outcomes, and increase power to detect differential subgroup effects, there may be biases. These biases include publication bias and data availability bias (i.e. if the collected studies are a biased subset of all eligible studies [41]), which may hamper the validity of IPD meta-analyses.

Publication bias may occur when studies with certain results (e.g. statistically

significant or clinically favorable results) are more likely to be published than other studies [42, 43]. This can generally lead to an overestimation of intervention effects [44]. In the POLARIS study that evaluated the effects of exercise interventions on QoL (Chapter 6) evidence was found for a significant publication bias for all eligible RCTs reporting on QoL, which overestimated the intervention effects by 28%. However, the RCTs included in the IPD meta-analysis were a representative sample of all published studies. No evidence for publication bias was found in the IPD meta-analysis that investigated the effects of psychosocial interventions on QoL (Chapter 7).

Data availability bias may occur when investigators of eligible studies are not willing or able to share the data of their study for an IPD meta-analysis. This situation leads to a set of available studies that may not reflect the entire evidence base [45]. For POLARIS, 49% of the eligible RCTs on exercise and 36% of the eligible RCTs on psychosocial interventions were included in the IPD meta-analyses, which may limit the generalizability of the results [46]. However, no significant differences in effect sizes were found between studies that were included in the IPD meta-analysis and those not included. This indicates that the studies included for both the analyses on exercise interventions as well as psychosocial interventions were a representative sample of the published studies, at least in terms of effects found in these studies.

Generalizability

The response rate of each RCT included in the POLARIS study may influence the generalizability of our findings. Patients who declined participation in the RCTs may be less interested in or motivated for exercise and/or psychosocial intervention [47, 48]. Previous studies that examined differences in characteristics between patients with cancer who participated in exercise trials and those that declined participation reported no differences in exercise levels between participants and non-participants to an exercise trial [49-51]. Differences were found in demographic characteristics, such that participants were more likely to be younger [49] and to have higher education levels [50, 51]. A previous systematic review that studied differences in characteristics between patients with cancer who participated in psychosocial interventions and those that declined participation showed no differences in

demographic (age, sex) and clinical characteristics (cancer type) [48]. Besides, most RCTs that examined psychosocial intervention effects included participants that were more likely highly educated, wealthier, and Caucasian patients with cancer [52]. Furthermore, the majority of studies evaluating the effects of exercise and psychosocial interventions have been conducted in patients with breast cancer or prostate cancer who were treated with curative intent [53, 54]. Due to differences in disease and treatment trajectories, results may not be generalizable to other (less common) cancer patient populations, such as patients with glioma, esophageal, head and neck and ovarian cancer, and patients with metastatic disease.

Clinical implications

The results of the POLARIS study showed that exercise interventions, and particularly those that are (partly) supervised, have significant beneficial effects on QoL and physical function in various subgroups of patients with cancer with different demographic and clinical characteristics, both during and after treatment. These findings support and strengthen the evidence base for current national and international exercise recommendations that all patients with cancer should be physically active during and after cancer treatment [54-61]. The results of the POLARIS study also suggest that psychosocial interventions are effective for improving QoL, emotional function, and social function in patients with cancer, both during and post treatment.

Although the findings presented in this thesis identified only a few moderators of intervention effects that would enable better targeting of interventions, it is and remains important to target exercise and psychosocial interventions to patients with cancer most in need for support. Some patients may be much better able to self-manage the consequences of cancer and its treatment (e.g. physical problems such as lower physical fitness, and psychological problems such as increased fatigue, anxiety, distress), while other patients may have a stronger need for referral to a monodisciplinary healthcare provider (e.g. physiotherapist, psychologist) or to multidisciplinary cancer rehabilitation [58, 62].

According to international exercise guidelines, patients with cancer should avoid inactivity and be as physically active as abilities and conditions allow [54]. If

possible, patients are recommended to exercise at least 150 minutes per week and include strength training exercises at least two days per week [54]. For patients who require supervision or who may need guidance on safe procedures, referral to a physiotherapist or exercise specialist may help [54]. The Dutch evidence-based guideline 'Medical specialist oncological rehabilitation', published in 2017 [58] recommends that patients with multiple related functional problems or with serious functional disorders with permanent disability should be referred to multidisciplinary cancer rehabilitation. In the case of a single problem, patient should be referred to a monodisciplinary healthcare provider. For example, patients with reduced physical function or psychological distress may go to a physiotherapist or a psychologist, respectively. As recommended by the guideline [58] these interventions should optimally fit the patient's characteristics, health state, needs, preferences, capabilities and opportunities. It is therefore important to know which existing programs works best, and for whom (that is, to identify important moderators of intervention effects). This thesis aimed to provide evidence on which moderating factors are of importance. Evidence from the studies conducted so far of which data were included in the POLARIS study (i.e. for patients with breast or prostate cancer who were treated with curative intent), indicates that targeting exercise interventions based on the studied demographic and clinical characteristics may not be useful for further improving QoL and physical function (Chapter 6). Therefore, exercise interventions can be offered in routine clinical cancer care for various subgroups of patients with cancer with different demographic and clinical characteristics, both during and after treatment. However, more research is needed to obtain insight into (possibly other) factors to improve individual patient care.

The Dutch guideline 'Screening for need psychosocial care' published in 2017 recommends routine screening and referral to specialized psychosocial care based on a patients' level of distress and/or need for care [63]. As recommended by the guideline, routine screening for distress is crucial at key points throughout the cancer continuum. Patients with distress experience lower QoL, have more difficulty making decisions about treatment, do not comply with treatment protocols, seek medical care more often leading to higher costs in health care, and are less satisfied with the medical care they receive [27, 64-66]. When distress is identified, the guideline recommends that an (specialized) oncology nurse of the treating team should take responsibility for coordinating proper assessment, referral and follow-up. Referral to psychosocial interventions may benefit from insight into the patient's

characteristics, health state, needs, preferences, capabilities and opportunities.

Based on the evidence from this thesis, targeting patients by screening for distress (e.g. depression, fatigue, cognitive problems, menopausal symptoms) is indeed important and likely results in higher effect sizes of psychosocial interventions (Chapter 7). In addition, coping skills training interventions may help to improve QoL for younger patients and for patients treated with chemotherapy. However, this thesis also showed that current coping skills training interventions may not address the needs of older patients. The supportive care needs of elderly patients should be identified and effective coping skills training interventions targeting this population should be developed.

Recommendations for future research

To further improve the effectiveness of exercise and psychosocial interventions for patients with cancer, interventions should be targeted to specific cancer populations with the highest needs, or tailored to specific characteristics of patient groups. This requires more knowledge of (I) the effects of exercise and psychosocial interventions in less common cancer populations, (II) optimal prescriptions for exercise and psychosocial intervention, (III) mediators of exercise and psychosocial intervention effects, (IV) strategies to optimize adoption, implementation and maintenance of exercise and psychosocial care at the patient as well as care giver levels, and (V) strategies to optimize data sharing and secondary analysis of harmonized single studies as a means to understand and predict intervention effects, inform policy makers, and maximize the benefits of exercise and psychosocial interventions for the individual patients with cancer [67-70].

Effects of exercise and psychosocial interventions in less common cancer populations

There is clear evidence that exercise and psychosocial interventions improve QoL in patients with breast and prostate cancer, and that it should be implemented as part of standard cancer care [3, 4, 10, 17]. However, as this evidence is generally based on breast, prostate, or mixed cancer groups, it is not yet known if similar exercise

and psychosocial interventions are feasible among patients with less common cancers such as glioma, esophageal, head and neck and ovarian cancer. Patients with glioma often experience cognitive deficits [71], and may therefore especially benefit from coping skills training to improve QoL [72]. In addition to fatigue, and muscle weakness, patients with head and neck cancer may experience distinct side effects from the cancer and its treatment, such as a dry mouth or throat, difficulty swallowing, and shoulder weakness and pain [73, 74], which may hamper participation in exercise. Information on how to manage disease-specific exercise barriers during standard cancer care may help these patients decreasing their side effects [75]. Compared to women with breast cancer, women with ovarian cancer have a distinct disease and treatment trajectory as ovarian cancer is often detected at a more advanced disease stage, has lower survival rates, and treatment often includes (interval) debulking surgery and (neo)adjuvant chemotherapy [76]. These patients may therefore need exercise and psychosocial interventions specifically customized their disease and treatment trajectory. By pooling data from similar exercise and psychosocial intervention studies, benefits of these interventions in less common cancers may be identified in larger samples. The POLARIS study that included IPD from multiple studies had the advantage to conduct IPD meta-analyses in specific cancer populations, not only from studies among patients with more common cancer, but also from studies that included patients with mixed cancer groups, including less common cancer populations. However, despite the advantage of pooling data from studies with mixed cancer types, allowing to increase the sample size, the sample sizes of these less common cancer types available in the POLARIS database remained small. Therefore, larger multicenter RCTs such as the interdisciplinary rehabilitation intervention among glioma patients [77], the Physical ExeRcise Following Esophageal Cancer Treatment (PERFECT) study in patients after surgery with curative intent [78], and the Physical Activity and Dietary intervention in OVArian cancer (PADOVA) study [79], are needed to confirm exercise intervention effects on QoL in these less common cancer populations, as they may differ from those with breast and prostate cancer due to differences in treatment trajectories. These and other studies conducted in less common cancer types can be included in the POLARIS database for further analyses.

Optimal prescriptions for exercise and psychosocial interventions

In order to optimize exercise prescriptions to improve QoL and physical function, more insight into the optimal exercise-related characteristics (i.e. frequency, intensity, type and time or duration of exercise) for patients with cancer is required. No differences in effects between types of exercise were found in this thesis, which is consistent with a previous meta-analysis on aggregate data that contains 32 more studies than our IPD meta-analyses [80]. Larger effects of supervised compared to unsupervised exercise interventions were found in this thesis and may be explained by a more demanding exercise prescription, a higher compliance to the prescribed exercise intervention, access to better equipment with more adjustment and performance feedback, the attention and support of the exercise physiologist delivering the intervention, and possibly social interaction with other participants [81]. The lack of significant differences in exercise effects across exercise-related characteristics in the current thesis might have resulted from little variation in these characteristics across studies that assessed supervised exercise interventions, as most of these studies investigated the effect of at least moderate-vigorous-intensity aerobic exercise with or without resistance exercise. However, there is some evidence that the effects of exercise vary by exercise frequency, intensity, type and duration [9, 82, 83]. Previous head-to-head comparisons of exercise-related characteristics indicated a dose response effect of aerobic exercise on physical function but not on QoL during treatment in patients with breast cancer [83], larger effects of resistance exercise than aerobic exercise compared with usual care on QoL in patients with prostate cancer [82], and larger effects of high intensity compared to low-moderate intensity exercise post treatment in a population with mixed cancer types [9]. Therefore, more adequately powered, high quality RCTs that directly compare exercise-related characteristics are warranted to define optimal exercise prescriptions on a given outcome, for a given cancer type, and in a particular phase of the cancer trajectory (e.g. during treatment, after treatment, end of life [84]).

In order to optimize the effects of psychosocial interventions, insight into the intervention-related characteristics such as delivery format (e.g. individual, group or couple therapy), method (e.g. face-to-face, telephone, or web-based), profession (e.g. psychologist versus nurse) and techniques, (e.g. behavioral activation, cognitive restructuring, problem-solving, relaxation training,) for patients with

cancer is required [85]. A previous RCT in patients with advanced cancer and their caregivers that investigated the optimal dose of a psychosocial intervention, found no differences in effects on QoL, emotional function and social function between a brief psychosocial program (that consisted of three contacts) and an extensive psychosocial program (that consisted of six contacts) [86]. However, the RCT also suggest that the optimal intervention dose may depend on which outcome is targeted for change. In addition, a previous RCT that examined the efficacy of Internet-based cognitive behavioral therapy for severe fatigue in patients with breast cancer [87], found that the effectiveness on severe fatigue was not significantly different from face-to-face cognitive behavioral therapy [88, 89]. More head-to-head comparisons of psychosocial intervention-related characteristics and techniques are needed to personalize psychosocial interventions on a given outcome.

Mediators of exercise and psychosocial intervention effects

To improve the effectiveness of exercise and psychosocial interventions on QoL, it is important to gain more knowledge ofthe working mechanisms of an intervention (i.e. intervention mediators) [1, 90, 91]. Insight into mediators of exercise and psychosocial interventions is important for identifying and subsequently targeting critical intervention components to improve effectiveness and efficiency and to reduce the costs [92, 93]. Although the current thesis showed that cardiorespiratory fitness is an important intervention target when aiming to reduce fatigue and improve physical function, and that muscle strength and function might be important intervention targets when aiming to reduce fatigue (Chapter 3), other psychosocial factors, such as reduced sleep quality, mastery and self-efficacy may also mediate the effect of exercise on fatigue [94, 95]. In addition, exercise interventions are specially focused on physical dimensions of QoL, whereas QoL also comprises emotional and social function [96]. Consequently, only improving or maintaining components of physical fitness (which exercise interventions generally aim for [94]) might not be sufficient and concepts other than or additional to physical fitness (such as emotional and social function) should be taken into account when aiming to improve QoL. In contrast, psychosocial interventions that aim to improve distress (e.g. depression, fatigue, cognitive problems, menopausal symptoms) showed beneficial effects on QoL, suggesting a role for improving emotional and social

domains of QoL.

In addition to psychosocial mediators, biological factors may mediate the effect of exercise on fatigue and QoL [97]. The association between elevated concentrations of C-reactive protein [98] and pro-inflammatory cytokines [99, 100] and cancer-related fatigue has been suggested in earlier studies. Exercise may lower these concentrations [101-104], and thereby reducing fatigue, and improve QoL. Future studies among patients with cancer should further explore anti-inflammatory effects of exercise and their mediating role on reducing fatigue and improve QoL, and focus how exercise can improve clinical outcomes such as tumour growth and (disease-free) survival as this would likely help adopting exercise as standard clinical practice [105].

Optimizing adoption, implementation and sufficient maintenance of exercise and psychosocial care

The RE-AIM (reach, efficacy, adoption, implementation, maintenance) framework sensibly argues that true (population) effectiveness of interventions is dependent on the efficacy as well as on how many patients adhere to the intervention program [106, 107]. To improve the effectiveness of the intervention, it is therefore essential to improve the adherence of these exercise and psychosocial interventions. Regarding exercise interventions, the association between several demographic (smoking, alcohol consumption), clinical (obesity) and psychosocial factors (self-efficacy, psychological distress), and exercise adherence has been suggested in earlier studies [50, 108]. However, more research is needed whether other factors such as social and environmental factors and the role of cancer treatment may play a role [50, 108]. Furthermore, as health behavior change theory-based interventions have shown to be more effective in changing behavior than non-theory based interventions [109], incorporation of these theories may further assist with adoption and maintenance of exercise and psychosocial interventions [50, 110]. Health behavior change theories may especially inform how the patients' personal motivation and abilities can be strengthened for participation in intervention programs [111, 112]. This is needed as 32-65% of eligible patients do not participate in exercise or psychosocial interventions in the studies conducted to date [50, 83, 86, 113, 114]. Previous studies suggested that exercise participation

may improve when exercise interventions are focused on intrinsic motivation, social support, self-efficacy, perceived benefits (in the long term), and perceived barriers [49, 50, 115, 116]. In order to improve the opportunities for participation in exercise and psychosocial interventions, interventions should be offered in a convenient manner to patients with cancer and supported by well-informed and trained health professionals.

Furthermore, for optimal implementation of exercise and psychosocial interventions in cancer care it is important to get insight in the cost-effectiveness of these interventions. Given the shortage of healthcare resources and the increasingly tight funding of healthcare systems, it is vital that exercise and psychosocial interventions be evaluated not only in terms of efficacy in symptom reduction and improving QoL (which evidence has been shown in the current thesis), but in economic terms as well [117]. Earlier studies suggest that offering exercise and psychosocial intervention to patients with cancer can be cost-effective [9, 116, 118-121]. However, as studies differed regarding types of exercise and psychosocial care and patient populations, future studies should provide more clear information as to which types of exercise and psychosocial inventions are most likely to be cost-effective and for whom.

Optimal data sharing

The POLARIS database has been developed in which IPD from – so far – 57 RCTs are harmonized to conduct IPD meta-analyses to evaluate the effects of exercise and psychosocial interventions on QoL in patients with cancer, and to identify moderators of intervention effects. Furthermore, this collection of datasets allows studying the effects and moderators of exercise and psychosocial interventions on other relevant outcomes than QoL including fatigue, sleep, and distress [122]. However, gathering IPD from principal investigators from the original study showed to be a timely endeavor. Delays occurred when these principal investigators did not respond to initial requests, or did not have the time to prepare their data for data sharing, or when legal issues needed to be resolved before data could be shared [123]. Of all 136 identified RCTs for POLARIS, IPD was not available for 45 RCTs, principal investigators of 27 RCTs did not respond to our request after a number of attempts, and principal investigators from another 7 RCTs had no approval from

their institute/university to share their IPD. Consequently, at the time of analyses, IPD had been obtained from 57 RCTs (42% or the total number of RCTs identified at the time), which is lower than the mean of 64% of all eligible studies that researchers usually obtain for IPD meta-analysis [124]. These results show that there is an urgent need to facilitate the data stewardship (i.e. a collection of data management methods covering acquisition, storage, aggregation, and de-identification, and procedures for IPD release and use [125]) supporting the reuse of IPD from exercise and psychosocial interventions among patients with cancer. To facilitate good data stewardship and to promote open science, a broad community of international stakeholders have developed the Findable, Accessible, Interoperable, Reusable (FAIR) Data principles [126]. When publishing data, authors should comply to these principles when maximizing the reusability of their datasets. The FAIR Data principles first posit that each study should be registered or indexed in a searchable resource, so that they can be located ('Findable'). For POLARIS, we identified eligible RCTs via systematic searches in four electronic databases (PubMed, EMBASE, PsycINFO, and CINAHL), reference checking of systematic reviews, meta-analyses, and personal communication with collaborators, colleagues, and other experts in the field. Principal investigators from eligible RCTs were invited to join the POLARIS consortium and share their IPD. Second, the FAIR data principles recommends that each study should provide and thus make available relevant metadata from these datasets to interested researchers, for instance, on the types of variables, age groups under study, study design, measurement instruments used, time frame ('Accessible'). For POLARIS, principal investigators that expressed interest in data sharing were asked to fill in a data request form where questions needed to be answered on their metadata (e.g. study design, contact details principal investigator(s)), and which IPD they want to share. Third, according to FAIR the IPD should be 'Interoperable' and thus use a consistent data format and classification for knowledge representation. The datasets from the individual studies included in POLARIS were imported in a data harmonization platform (Chapter 5) where they were re-coded according to standardized protocols and harmonized. Finally, IPD should be 'Reusable', that is, made available to other researchers [126]. For POLARIS, the harmonized datasets were, and are, used to study the effects and moderators of exercise and psychosocial interventions on QoL, fatigue, sleep, and distress, and are made available to other researchers [122]. Thus, the POLARIS study showed that it is possible to successfully undertake IPD meta-analyses to evaluate the effects of exercise and psychosocial

interventions on QoL in patients with cancer, and to identify moderators of intervention effects. However, the reusability of datasets was limited to the 42% of all identified datasets to which access was granted. Therefore, different approaches should be investigated in the future how to encourage principal investigators to share their dataset for IPD meta-analysis. Principal investigators should publish an open and freely accessible study protocol for easily retrieving metadata from their study such as types of variables, age groups under study, study design, measurement instruments used, and time frame. Besides, principal investigators should be clear which IPD will be made (openly) available for interested researchers, legal and ethical issues should be resolved, and IPD should be clearly stored after finalizing their study. The POLARIS study applies to these FAIR data principles, as publications from the POLARIS study can be find through search approaches ('Findability'). It is possible to retrieve the metadata from these datasets on the types of variables, age groups under study, study design, measurement instruments used, and time frame ('Accessibility'). The IPD available in the POLARIS study use a consistent data format and classification for knowledge representation ('Interoperable'), and IPD are made available to other researchers ('Reusability'). Complying to the FAIR principles will help the reusability of relevant IPD. This will help future research to understand and predict intervention effects, inform policy makers, and maximize the benefits of exercise and psychosocial interventions for the individual patients with cancer.

Conclusion

This thesis has the following conclusions. First, the effects of a group-based exercise intervention on global QoL were larger in patients who received radiotherapy, and particular those who received a combination of chemotherapy and radiotherapy, and in patients with higher levels of fatigue at baseline (i.e. prior to the exercise intervention). Second, the current thesis showed that exercise, and particular those with a supervised component, has small but significant beneficial effects in improving QoL and physical function across subgroups of patients with cancer with different demographic and clinical characteristics, both during and after treatment. Third, psychosocial interventions significantly improved QoL, emotional function and social function, but overall effects were small. Significant differences in effects of different types of psychosocial interventions were found, with largest effects of

psychotherapy compared to coping skills training and information provision. The effects of coping skills training were moderated by age, treatment type, and targeted interventions. Effects of psychotherapy on emotional function may be moderated by cancer type, but these analyses were based on two RCTs with small sample sizes of some cancer types. Fourth, beneficial effects of exercise on global QoL and physical function in patients with cancer were mediated by increased cardiorespiratory fitness, and subsequent reductions in fatigue. Finally, IPD meta-analyses benefits from a flexible data harmonization platform that facilitates harmonizing data during data collection, especially when the number of studies and variables is large.

In conclusion, the results of the current thesis showed that exercise and psychosocial interventions have significant beneficial effects on QoL. However, the effects differed by several demographic, clinical, personal, and intervention-related characteristics. More research is needed how to fully implement these interventions into clinical oncology practice and to make exercise and psychosocial interventions an essential component of cancer care that optimally fit the patient's characteristics, health state, needs, preferences, capabilities and opportunities.

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English summary

Nederlandse samenvatting

List of publications

Dankwoord

About the author

English summary

In the last decades, the overall survival rate of cancer has increased substantially, due to advances in early cancer detection (i.e. diagnosis and screening) and more effective treatments. Unfortunately, many patients with cancer face physical and psychosocial problems, including cancer-related fatigue, lower cardiorespiratory fitness and muscle strength, and increased risk of anxiety and depression. These physical and psychosocial problems have a negative impact on the patients' health-related quality of life (QoL). **Chapter 1** introduces exercise and psychosocial interventions as promising strategies to reduce or limit physical and psychosocial problems that are associated with a cancer diagnosis and treatment. In previous meta-analyses, significant and positive effects on QoL were observed, although the mean effect sizes were small-to-moderate. One possible explanation for the small effect sizes of exercise and psychosocial interventions is that these interventions are typically offered to a heterogeneous group of patients with cancer and are not targeted to specific patients. Such a 'one-size-fits all' approach may explain the modest effects of these interventions that have been reported. Therefore, these interventions should be better targeted and tailored to specific characteristics of patients. To be able to shift from this 'one-size-fits-all' approach to more personalized exercise and psychosocial interventions, it is important to identify which subgroups of patients respond best to these interventions. Furthermore, to improve the effectiveness of exercise and psychosocial interventions on quality of life (QoL) among patients with cancer, insights in the working mechanisms of an intervention are needed. Therefore, this thesis aimed to investigate the effects of exercise and psychosocial interventions on QoL in patients with cancer during and after cancer treatment and to identify demographic, clinical, personal and intervention-related moderators of these intervention effects. Further, this thesis investigated some possible mechanisms underlying the effects of exercise interventions on QoL. Finally, this thesis aimed to build a flexible data harmonization platform that facilitates harmonizing raw individual patient data (IPD) of original studies for meta-analyses purposes, where such data harmonization can already start during collection of the data from the original studies.

Chapter 2 explored possible demographic (age, sex, education level),

clinical (type of treatment, time since treatment, presence of comorbidity), and psychological (fatigue, self-efficacy, symptoms of depression and anxiety) moderators of the effect of group-based physical exercise on global QoL in patients with cancer who completed treatment. The results of this single study suggest that the effects of a group-based exercise intervention on global QoL in patients after cancer treatment were larger for patients who received radiotherapy, and in particular, in those who received a combination of chemotherapy and radiotherapy, and in patients with higher levels of fatigue at baseline (i.e. prior to the exercise intervention). No moderator effects were found for age, sex, education level, marital status, employment status, time since treatment, presence of comorbidity, self-efficacy, depression, and anxiety. However, single studies are generally not powered to analyze moderators of intervention effects and to conduct subsequent stratified analysis. Therefore, studies with much larger sample sizes, such as meta-analyses of raw IPD, are needed to confirm these findings.

Chapter 3 studied the hypothesis that a 12-week resistance and endurance exercise program improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and improving global QoL and physical function among patients with cancer who completed curative treatment, including chemotherapy. The results of the study showed that cardiorespiratory fitness mediated the exercise intervention effects on physical fatigue, global QoL and physical function. Thus, improving cardiorespiratory fitness could be an important intervention target to reduce fatigue and to improve patient's global QoL and physical function. Furthermore, higher hand-grip strength was associated with lower physical fatigue and better lower body muscle function with lower general and physical fatigue. This indicates that muscle strength and function might be important intervention targets when aiming to reduce fatigue. However, muscle strength and function did not mediate the exercise effects on fatigue and physical function, because no significant effect of the exercise intervention was found on this outcome. The lack of significant effects of exercise on muscle strength and function may be related to the choice of instruments used to assess the outcomes. Finally, reducing fatigue was found to be important to improve global QoL and physical function, and exercise is an effective strategy to do so.

Chapter 4 describes the design of the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study that is used for IPD meta-

analyses. POLARIS included randomized controlled trials (RCTs) that evaluated the effects of exercise interventions and/or psychosocial interventions on QoL compared to a wait-list, usual care or attention control group in adult patients with cancer. One-hundred thirty-six relevant studies were identified though database searches (Pubmed, EMBASE, PscyINFO, and CINAHL), via reference checking of examined systematic reviews, meta-analyses, and via personal communication with collaborators, colleagues, and other experts in the field. Subsequently, the principal investigator of each eligible study was invited to share their IPD with the POLARIS study. The main outcome measures were general/overall QoL and specific QoL domains (physical function for exercise interventions, and emotional and social function for psychosocial interventions). Linear mixed-effect model analyses were used to study intervention effects on the post-intervention values of QoL, physical, emotional and social function. We studied moderator effects by testing interactions with the intervention for demographic, clinical, personal, and intervention-related characteristics, and conducted subsequent stratified analyses for significant moderator variables.

Chapter 5 describes a flexible data harmonization platform that facilitates harmonizing data during data collection for use in IPD meta-analysis. The data harmonization platform uses Microsoft Access as front-end application and with a relational database management system such as Microsoft Structured Query Language (SQL) Server or MySQL as back-end application. This platform is the first data harmonization platform that allows starting data harmonization already during data collection, which is time efficient, especially when the number of studies is large. Furthermore, the data harmonization platform allows to store, prepare, and harmonize IPD within one transparent platform. The harmonization process is facilitated by transparent interfaces, which makes the platform easy in use. Finally, the data harmonization platform has the ability to export harmonized IPD and corresponding data dictionary to the statistical program SPSS for further analysis.

Chapter 6 evaluated the effects of exercise on QoL and physical function in patients with cancer, and studied possible demographic, clinical, intervention-, and exercise-related moderators of intervention effects with IPD meta-analysis. This study found that exercise, and particularly exercise with a supervised component, effectively improved QoL and physical function. No moderator effects on QoL and physical function were found for demographic (age, sex, marital status, and education

level), clinical (body mass index, type of cancer, the presence of distant metastases, and type of treatment), and other intervention- and exercise related characteristics (timing and duration of intervention, type of control group, and exercise frequency, intensity type, and session duration). These findings suggest that targeting exercise interventions based on demographic and clinical characteristics may not be useful for further improving QoL and physical function.

Chapter 7 evaluated the effects of psychosocial interventions on QoL, emotional function and social function among patients with cancer, and aimed to identify demographic, clinical, personal, and intervention-related moderators of intervention effects with IPD meta-analysis. Results showed that psychosocial interventions have small but significant beneficial effects on QoL, emotional function, and social function. Psychotherapy appeared to have larger effects compared to coping skills training and providing information, but this conclusion was based on two psychotherapy intervention studies that investigated interventions that specifically targeted patients with psychological distress. The effects of coping skills training were moderated by age, treatment type, and targeted interventions (i.e. targeted to patients with distress). The effects of coping skills training on emotional and social function were larger among younger patients. Further, type of cancer treatment was a significant moderator of the effect of coping skills training, such that larger effects on QoL and emotional function were found in patients treated with chemotherapy, and larger effects on social function were found in patients with breast cancer who did not receive hormone therapy, and in patients who had surgery. Furthermore, effects of coping skills training on QoL were larger in studies that targeted patients with distress. The effects of psychotherapy on emotional function may be moderated by cancer type, with significant effects for patients with breast and hematological cancer, but these analyses were based on two RCTs with small sample sizes of some cancer types. This study emphasizes the need for developing a coping skills training tailored to the specific needs of elderly patients, and highlights the importance of targeting psychosocial interventions to patients with distress.

Chapter 8 presented and interpreted the main findings of this thesis. Furthermore, the methodological considerations including statistical power, study design, primary outcome, potential sources of bias in IPD meta-analyses, and generalizability were discussed. Overall, the results in this thesis support

and strengthen the evidence base for current national and international exercise recommendations that all patients with cancer should be physically active during and after cancer treatment. The results of the POLARIS study also suggest that psychosocial interventions are effective for improving QoL, emotional function, and social function in patients with cancer, both during and after treatment. Besides, targeting patients with distress (e.g. depression, fatigue, cognitive problems, menopausal symptoms) is important and likely results in higher effect sizes of psychosocial interventions. Additionally, coping skills training interventions may help to improve QoL for younger patients and for patients treated with chemotherapy. To further improve the effectiveness of exercise and psychosocial interventions for patients with cancer, interventions should be targeted to specific cancer populations with the highest needs, or tailored to specific characteristics of patient groups. Therefore, the studies presented in this thesis suggest that future multicenter RCTs should investigate if similar exercise and psychosocial interventions are feasible and effective in patients with less common cancers such as glioma, esophageal, head and neck and ovarian cancer, as current evidence is generally based on breast, prostate, or mixed cancer groups. Second, future studies should study differences in effects between different exercise-related characteristics and psychosocial intervention-related characteristics to optimize prescriptions for exercise and psychosocial interventions to improve QoL. Third, future studies should focus on identifying mediators of exercise and psychosocial interventions for identifying and subsequently targeting critical intervention components to improve effectiveness and efficiency, and to reduce the costs. Fourth, more research is needed whether social and environmental factors and cancer treatment may play a role in exercise adherence. Besides, future studies should provide more clear information as to which types of exercise and psychosocial interventions are most likely to be cost-effective and for whom. Finally, future studies should comply to the Findable, Accessible, Interoperable, Reusable (FAIR) data principles for data stewardship. This will help future research to understand and predict intervention effects, inform policy makers, and maximize the benefits of exercise and psychosocial interventions for the individual patients with cancer.

Nederlandse samenvatting

In de laatste decennia is de overlevingskans van kanker aanzienlijk toegenomen als gevolg van verbetering in vroege detectie van kanker en de behandeling ervan. Helaas hebben veel patiënten met kanker te kampen met lichamelijke en psychosociale problemen, waaronder toename in vermoeidheid, verminderde cardiorespiratoire fitheid en spierkracht en meer angst en depressie. Deze problemen hebben een negatief effect op de kwaliteit van leven van de patiënt. Hoofdstuk 1 introduceert fysieke trainings- en psychosociale interventies als veelbelovende strategieën om lichamelijke en psychosociale problemen, als gevolg van de diagnose en behandeling van kanker, te verminderen en/of te beperken. In eerdere meta-analyses werden significante en positieve effecten van het toepassen van de interventies op kwaliteit van leven gevonden, al waren de gemiddelde grootte van de effecten klein tot matig. Om het effect te vergroten, is het belangrijk dat fysieke trainings- en psychosociale interventies gerichter aangeboden worden aan specifieke patiëntengroepen. Hiervoor is kennis nodig welke interventie het meest effectief is om de kwaliteit van leven te behouden of te verbeteren, en voor wie en wanneer deze interventie effectief is. Om de effecten van fysieke trainings- en psychosociale interventies op de kwaliteit van leven bij patiënten met kanker te verbeteren is bovendien inzicht nodig in de werkingsmechanismes van een interventie. Dit proefschrift heeft als doel om inzicht te krijgen in de effecten van fysieke trainings- en psychosociale interventies op de kwaliteit van leven bij patiënten met kanker tijdens en na de behandeling en of de effecten van deze interventies op de kwaliteit van leven worden beïnvloed door demografische, klinische, persoonlijke en interventie-gerelateerde kenmerken. Ook wordt de hypothese getoetst dat een kracht- en duurtrainingsprogramma resulteert in een verbeterde fysieke fitheid, welke vervolgens leidt tot minder vermoeidheid en een betere kwaliteit van leven en fysiek functioneren. Tot slot beschrijft dit proefschrift de ontwikkeling en het gebruik van een data harmonisatie platform dat het mogelijk maakt om ruwe individuele patiëntengegevens van originele studies te harmoniseren tijdens de dataverzameling voor meta-analyses.

In **Hoofdstuk 2** is onderzocht of het effect van een fysieke trainingsinterventie op de kwaliteit van leven van patiënten na afloop van de behandeling van kanker werd beïnvloed door demografische (leeftijd, geslacht en opleidingsniveau), klinische (type behandeling, tijd sinds behandeling en aanwezigheid van comorbiditeiten), en psychologische (vermoeidheid, eigen-effectiviteit en symptomen van angst en

depressie) kenmerken. De resultaten van deze studie suggereren dat het effect van fysieke trainingsinterventie aangeboden in een groep groter waren op de kwaliteit van leven voor diegenen die radiotherapie kregen, en in het bijzonder van patiënten die zowel chemotherapie als radiotherapie kregen. Daarnaast was er een groter effect voor patiënten met meer vermoeidheid voorafgaand aan de fysieke trainingsinterventie. Het effect werd niet beïnvloed door leeftijd, geslacht, opleidingsniveau, burgerlijke staat, werkstatus, tijd sinds behandeling, aanwezigheid van comorbiditeiten, eigen effectiviteit, angst en depressie. Individuele studies hebben echter onvoldoende statistische *power* om verschillen in trainingseffecten op de kwaliteit van leven tussen patiënten met verschillende kenmerken te onderzoeken en om gestratificeerde analyses te kunnen doen. Daarom zijn studies met grotere steekproeven nodig om de bevindingen van deze studies te bevestigen, zoals meta-analyses met individuele patiëntengegevens.

Hoofdstuk 3 bestudeert de hypothese dat een kracht- en duurtrainingsprogramma bij patiënten met kanker kort na afronding van een in opzet curatieve behandeling met chemotherapie, resulteert in een verbeterde fysieke fitheid, en vervolgens leidt tot minder vermoeidheid en een verbeterde kwaliteit van leven en fysiek functioneren. De trainingseffecten op de fysieke vermoeidheid, de algemene kwaliteit van leven en het fysiek functioneren werden inderdaad deels verklaard door een verbeterde cardiorespiratoire fitheid. Daarom kan het verbeteren van cardiorespiratoire fitheid bij patiënten met kanker een belangrijk doel zijn van een interventie om daarmee de vermoeidheid te verminderen of de kwaliteit van leven en het fysiek functioneren te verbeteren. Daarnaast was een hoge handknijpkracht en een betere spierfunctie van de benen geassocieerd met een lagere vermoeidheid, en was een betere spierfunctie van de benen geassocieerd met een hoger fysiek functioneren. Deze resultaten geven aan dat het verbeteren van spierkracht en spierfunctie belangrijk kan zijn om vermoeidheid te verminderen. Tot slot toonden de resultaten aan dat vermindering van vermoeidheid belangrijk is voor de kwaliteit van leven en het fysiek functioneren, en dat dit bereikt kan worden door fysieke training.

Hoofdstuk 4 beschrijft de opzet van de 'Predictie van OptimaLe kAnker RevalIdatie en psychosociale Steun' (POLARIS)-studie. De POLARIS-studie verzamelde gerandomiseerde interventiestudies die de effecten van fysieke trainings- en/of psychosociale interventies onderzochten op de kwaliteit van leven van patiënten met kanker ten opzichte van een wachtlijst controlegroep, gebruikelijke zorg of

een aandacht controlegroep. Er werden 136 relevante studies geïdentificeerd in vier onlinedatabases (Pubmed, EMBASE, PscyINFO en CINAHL), via referenties van eerdere systematische reviews en meta-analyses, en via persoonlijke communicatie met medewerkers, collega's en andere experts in het veld. Vervolgens werd de hoofdonderzoeker van elke geschikte studie uitgenodigd om zijn of haar ruwe data te delen met de POLARIS-studie. De belangrijkste uitkomstmaten waren de algemene kwaliteit van leven en specifieke domeinen van kwaliteit van leven (zoals fysiek functioneren voor fysieke trainingsinterventies, en emotioneel- en sociaal functioneren voor psychosociale interventies). Met behulp van multilevel analyses (*linear mixed-effect model analyses*) werden de effecten van de interventie op de kwaliteit van leven, en het fysiek-, emotioneel- en sociaal functioneren direct na afloop van de interventie onderzocht. Verschillen in interventie effecten tussen patiënten met verschillende demografische, klinische, persoonlijke en interventie-gerelateerde kenmerken werden onderzocht met behulp van interactietermen.

Hoofdstuk 5 beschrijft een data harmonisatie platform dat het mogelijk maakt om gegevens van individuele studies voor een meta-analyse van individuele patiëntengegevens te harmoniseren tijdens dataverzameling. Het data harmonisatie platform gebruikt Microsoft Access als *front-end* applicatie en een databasemanagementsysteem zoals *Microsoft Structured Query Language* (SQL) *Server* of MySQL als *back-end* applicatie. Dit platform is het eerste platform voor gegevensharmonisatie dat gebruikt kan worden vanaf het begin van het verzamelen van gegevens, wat tijdsefficiënt is, vooral wanneer het aantal studies groot is. Bovendien maakt het data harmonisatie platform het mogelijk om individuele patiëntengegevens op te slaan, voor te bereiden en te harmoniseren binnen één overzichtelijk platform. Het harmonisatieproces wordt vergemakkelijkt door overzichtelijke interfaces, waardoor het platform eenvoudig in gebruik is. Ten slotte heeft het data harmonisatie platform de mogelijkheid om geharmoniseerde individuele patiëntengegevens en bijbehorend codeboek te exporteren naar het statistische programma SPSS voor verdere analyse.

Hoofdstuk 6 presenteert de resultaten van een meta-analyse van individuele patiëntengegevens waarin werd onderzocht of de effecten van fysieke trainingsinterventies op de kwaliteit van leven en fysiek functioneren werden beïnvloed door demografische, klinische, en interventie-gerelateerde kenmerken of door specifieke trainingsvoorschriften. De resultaten laten zien dat een fysieke trainingsinterventie tijdens of na de behandeling van kanker, en met

name van fysieke training interventies die geheel of gedeeltelijk gesuperviseerd waren, leidt tot een significant betere kwaliteit van leven en fysiek functioneren in vergelijking met de controlegroep. Er is geen bewijs gevonden dat de mate van verbetering afhankelijk was van demografische (leeftijd, geslacht, burgerlijke staat of opleidingsniveau), klinische (BMI, type kanker, aanwezigheid van gemetastaseerde ziekte of type behandeling), andere interventie-gerelateerde kenmerken (interventie duur en timing en soort controlegroep) en specifieke trainingsvoorschriften (trainingsfrequentie, -intensiteit of -type, sessieduur). De gevonden resultaten suggereren daarmee dat een fysieke trainingsinterventie specifiek gericht op patiënten met bepaalde demografische en klinische kenmerken niet van toegevoegde waarde is voor verder behoud of verbetering van de kwaliteit van leven en het fysiek functioneren van patiënten met kanker.

Hoofdstuk 7 presenteert de resultaten van een meta-analyse van individuele patiëntengegevens waarin werd onderzocht of de effecten van psychosociale interventies op de kwaliteit van leven en het emotioneel- en sociaal functioneren werden beïnvloed door demografische, klinische, persoonlijke en interventie-gerelateerde kenmerken. De resultaten toonden aan dat psychosociale interventies kleine maar significante positieve effecten hebben op de kwaliteit van leven en het emotioneel- en sociaal functioneren. Psychotherapie leek grotere effecten te hebben in vergelijking met *coping skills training* (zogenaamde interventies die bedoeld zijn om (verschillende) cognitieve en gedragsmatige technieken of vaardigheden te trainen) of informatievoorziening. Deze bevinding was echter gebaseerd op twee studies waarin de effectiviteit van psychotherapeutische interventies werd onderzocht bij patiënten met psychische *distress*.

De effecten van *coping skills training* werden beïnvloed door leeftijd, of de interventies gericht waren op patiënten met psychische distress en het type behandeling. Zo waren de effecten van *coping skills training* op emotioneel- en sociaal functioneren groter bij jongere patiënten. Daarnaast waren de effecten van *coping skills training* op de kwaliteit van leven groter in studies die uitgevoerd werden bij patiënten met psychische *distress*. Verder werd het effect van *coping skills training* beïnvloed door het type behandeling: de effecten op de kwaliteit van leven en het emotioneel functioneren waren allereerst groter bij patiënten die werden behandeld met chemotherapie. Ook waren de effecten op het sociaal functioneren groter bij patiënten die een operatie hadden ondergaan en bij patiënten met borstkanker zonder hormoontherapie.

De effecten van psychotherapie op het emotioneel functioneren werden beïnvloed door het type kanker, met significant grotere effecten voor patiënten met borst- en hematologische kanker. Echter, deze bevindingen zijn gebaseerd op twee gerandomiseerde studies met kleine patiënten aantallen van een aantal type kankers. De resultaten van de meta-analyse benadrukken de noodzaak om een *coping skills training* te ontwikkelen die is afgestemd op de specifieke behoeften van oudere patiënten, en ze benadrukken het belang van psychosociale interventies die specifiek gericht zijn op patiënten met psychische *distress*.

Hoofdstuk 8 presenteert en interpreteert de belangrijkste bevindingen van dit proefschrift. Tevens bespreekt dit hoofdstuk de methodologische overwegingen, waaronder de statistische *power*, de studieopzet, de primaire uitkomstmaat, potentiële bronnen van bias in meta-analyses van individuele patiëntengegevens en de generaliseerbaarheid van de resultaten. De resultaten in dit proefschrift ondersteunen en versterken de huidige nationale en internationale aanbevelingen dat alle patiënten met kanker fysiek actief moeten zijn tijdens en na de behandeling. De resultaten van de POLARIS-studie suggereren ook dat psychosociale interventies effectief zijn voor het verbeteren van de kwaliteit van leven, en het emotioneel- en sociaal functioneren van patiënten met kanker, zowel tijdens als na de behandeling. Bovendien is het belangrijk om psychsociale interventies specifiek aan te bieden aan patiënten met *distress* (bijvoorbeeld depressie, vermoeidheid, cognitieve problemen, symptomen van de menopauze), welke waarschijnlijk zullen resulteren in grotere effecten van psychosociale interventies. Bovendien kan *coping skills training* helpen om de kwaliteit van leven te verbeteren voor jongere patiënten en voor patiënten die worden behandeld met chemotherapie. Om de effectiviteit van fysieke trainings- en psychosociale interventies voor patiënten met kanker verder te verbeteren moeten toekomstige interventies gericht zijn op een specifieke patiëntenpopulatie met de meeste behoefte aan hulp of afgestemd zijn op specifieke kenmerken van patiënten. Toekomstige multicenter gerandomiseerde studies zouden moeten onderzoeken of vergelijkbare fysieke trainings- en psychosociale interventies haalbaar en effectief zijn bij patiënten met minder vaak voorkomende soorten kankers zoals glioom, slokdarmkanker, hoofd-halskanker en eierstokkanker, aangezien het huidige bewijs met name is gebaseerd op patiënten met borstkanker en prostaatkanker of populaties met verschillende diagnoses. Ook zouden toekomstige studies de verschillen in effecten op de kwaliteit van leven moeten bestuderen tussen verschillende voorschriften

van fysieke trainings- en psychosociale interventies om daarmee de voorschriften te optimaliseren. Verder zouden toekomstige studies zich moeten richten op het identificeren van de werkingsmechanismes van fysieke trainings- en psychosociale interventies die het effect van deze interventies kunnen verklaren. Kennis van belangrijke interventiecomponenten is nodig om de effectiviteit en de efficiëntie te verbeteren en de kosten te verlagen. Bovendien is er meer onderzoek nodig om te bepalen of sociale- en omgevingsfactoren en het type behandeling een rol kunnen spelen bij de therapietrouw van fysieke trainingsinterventies. Ook moeten toekomstige studies meer kennis opleveren over welk soort fysieke trainings- en psychosociale interventie het meest kosteneffectief is en voor wie. Ten slotte moeten toekomstige studies voldoen aan de richtlijnen van de Findable, Accessible, Interoperable, Reusable (FAIR) principes voor de manier van beschrijven, opslag en publicatie van wetenschappelijke data. Dit zal toekomstig onderzoek helpen om 1) beter inzicht te krijgen in de effecten van interventies, 2) beleidsmakers beter te kunnen informeren voor wie wat werkt, en 3) de effecten van fysieke trainings- en psychosociale interventies voor individuele patiënten met kanker te optimaliseren.

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Dankwoord

Dit proefschrift heb ik niet kunnen schrijven zonder de hulp van anderen. Mijn grootste dank gaat uit naar mijn copromotor Laurien en mijn promotoren Hans en Irma. Beste Laurien, dank voor al je hulp, steun, kritische noten en gelach. Dankzij jou heb ik dit mooie proefschrift kunnen schrijven. We hebben veel diepgaande discussies gehad, maar kon ook bij je terecht voor kleine vragen. Je passie, enthousiasme, intelligentie en je meelevendheid zorgden ervoor dat je voor mij de beste begeleider was die ik kon wensen. Beste Hans, dank voor je overkoepelende blik die je had en je kritische noot waar nodig. Zonder jouw hulp waren onze stukken nooit zo geworden zoals ze nu zijn wat oprecht een kudo verdient. Beste Irma, bedankt voor al je steun en betrokkenheid in de stukken. Bij alle artikelen heb je kritisch meegedacht en je aandacht voor zowel detail als het geheel hebben mij erg geholpen.

Ook wil ik de co-auteurs bedanken die hebben meegewerkt aan dit proefschrift. Allereerst de co-auteurs van de OncoRev studie. Anne May, Irene Korstjens, Ellen van Weert, Ilse Mesters, Bart van den Borne, Josette Hoekstra-Weebers, en Wynand Ros. Dank jullie wel voor het beschikbaar stellen van de data en het kritisch meedenken met het manuscript zodat we samen dit mooie paper over moderatie effecten hebben kunnen schrijven. Daarnaast de co-auteurs van de REACT studie. Caroline Kampshoff, leuk dat we het paper over mediatie effecten hebben kunnen schrijven. Mai Chinapaw, Willem van Mechelen, Francisca Galindo-Garre, en Goof Schep. Dank voor het kritisch meelezen van het paper, met jullie input is het een mooi paper geworden. Als laatste alle co-auteurs die hebben meegeschreven met de POLARIS papers. Dank jullie wel, Thank you, Danke, Takk, Tak, Tack, Merci, Gracias, for all your comments and insights in the field of exercise and psychosocial care in patients with cancer. Special thanks to the advisory board of POLARIS. Neil Aaronson, Kerry Courneya, Paul Jacobsen and Rob Newton, thank you for all your support and help in setting up the POLARIS study and critically reviewing all the papers.

Geachte leden van de beoordelingscommissie, prof. dr. Henk Verheul, prof. dr. Henk Stam, prof. dr. Remco de Bree, prof. dr. Pim Cuijpers, prof. dr. Raymond

Ostelo en dr. Floortje Mols. Bedankt dat jullie de tijd hebben genomen om mijn manuscript te lezen en te beoordelen.

Ik wil iedereen van de onderzoeksgroepen Samen Leven met Kanker en AXiON bedanken voor de fijne tijd samen. Dank voor al de leuke meetings en tussentijdse koffie momenten. Het congres naar Washington D.C. met de Samen Leven met Kanker groep staat nog steeds in mijn geheugen gegrift!

De secretaresses met wie ik veel contact heb gehad. Annette, Mieke en Sandra. Dank voor al jullie tijd en hulp wanneer ik die nodig had. Annette en Mieke, dank voor het keuvelen ‘s ochtends onder het genot van een espresso! De dag kon niet beter beginnen.

Data management, ICT en juridische zaken van de universiteit. Patrick, Lenny, Jeroen, Jan, Wim, Cees en Cuneyt. Dank jullie wel voor jullie expertise en ondersteuning van de POLARIS studie waar nodig.

Remco en Roel, heel fijn dat jullie mijn paranimfen willen zijn en mij bij willen staan op de grote dag. Bedankt voor jullie interesse.

Lieve familie en schoonfamilie. Bedankt voor jullie betrokkenheid en gezelligheid. Papa en mama, dank jullie wel voor jullie interesse in mijn proefschrift en fijn dat ik altijd bij jullie terecht kan. Hopelijk maakt de grote dag jullie nog trotser dan dat jullie al zijn. Meriem en Arjon, zo blij met jullie als zus en broer. Ik kon altijd bij jullie terecht voor een gezellig avondje of als oppas broertje voor Tobias, Anna, Daan en Broos zodat ik niet altijd aan mijn proefschrift hoefde te denken.

Lieve Mirjam, wat ben ik toch ontzettend blij met je. 2018 is ons jaar met de bruiloft, een nieuw huis en een mooi proefschrift. Je was er altijd voor me

wanneer ik je hulp nodig had bij een artikel en je input was zo ontzettend belangrijk wanneer ik ergens vastliep met schrijven. Jouw steun heeft ervoor gezord dat ik dit mooie proefschrift heb kunnen schrijven.

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Joeri Kalter was born on 4th of February, 1982 in Losser, the Netherlands. He obtained the HAVO diploma in 1999 and the VWO diploma in 2001 at the Twents Carmel College in Oldenzaal. He further graduated in physical therapy in 2007 at the Saxion University of Applied Sciences in Enschede. In 2007, he started working as a research assistent at the Technology, Health & Care Lectorate of the Saxion University of Applied Sciences in Enschede, where he assisted in different projects including the Functional Capacity Evaluations in the Cohort Hip and Cohort Knee study.

In 2008, he became a student at the VU University in Amsterdam. He completed his premaster Health Sciences in 2009 and his research MSc Lifestyle and Chronic Disorders in 2011. During his studies, he completed two scientific papers for this master program; 'Taping patients with clinical signs of subacromial impingement syndrome: the design of a randomized controlled trial' at the EMGO+ Institute in Amsterdam and 'the role of predictive factors on bone strength: the Nepean longitudinal study' at the George Institute for Global Health in Sydney, Australia. In addition, he was the chairman of the Committee Careerday Health Sciences Amsterdam 2010, and was a research assistent at the faculty of Earth and Life Sciences of the VU University in Amsterdam, where teached premaster students the beginnings of epidemiology.

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