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 of the 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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