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 through database searches (Pubmed, EMBASE, PsycINFO, 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.