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ENGLISH SUMMARY

Over the past decades survival rates in cancer survivors have improved significantly, as a result of improved screening and treatment. However, it is important to acknowledge that cancer and cancer treatment are associated with long-term physical and psychosocial problems. These problems include decreased cardiorespiratory fitness and muscle strength, increased risk of anxiety and depression, and/or severe feelings of fatigue, which negatively affects a patient's quality of life. **Chapter 1** of the thesis introduces supervised exercise as a promising strategy to assist cancer survivors in coping with, and recovering from, cancer and treatment related problems. Previous systematic reviews reported physical and psychosocial benefits of exercise among cancer survivors and highlighted the importance to define optimal exercise prescriptions in terms of frequency, intensity, type and time (i.e., FITT factors) of exercise. Furthermore, implementation of exercise interventions might be facilitated by a better understanding of the demographic, clinical, psychosocial, physical, and environmental factors that influence participation and exercise adherence among cancer survivors. Therefore, this thesis aimed to evaluate and compare the (cost-)effectiveness of a high intensity (HI) and a low-to-moderate intensity (LMI) exercise intervention on physical fitness and fatigue. In addition, the hypothesis was tested that resistance and endurance exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and consequently improving global quality of life (QoL) and physical function. Finally, this thesis aimed to identify demographic, clinical, psychosocial, physical, and environmental factors that are associated with exercise participation and exercise adherence in order to facilitate the development of effective and targeted interventions for cancer survivors.

Chapter 2 presents the design of the Resistance and Endurance exercise After ChemoTherapy (REACT) study, a multicenter randomized controlled trial (RCT) evaluating the effects on physical fitness and fatigue, and the cost-effectiveness of a HI exercise intervention compared to a LMI exercise intervention and a waiting list control (WLC) group in cancer survivors who had recently completed primary treatment with curative intent, including chemotherapy. Aiming to determine differences in effectiveness of different exercise intensities, both exercise interventions comprised similar exercise types, durations and frequencies, and only differed in exercise intensity. Both interventions included two one-hour exercise sessions per week during 12 weeks, supervised by a physiotherapist. Immediately after baseline assessments and randomization, participants in the HI and LMI exercise groups commenced their 12-week exercise intervention. Participants from the WLC group were also randomly allocated to HI

or LMI exercise, however they started exercising after the 12-week follow-up assessment. Consequently, at 64 weeks all participants had received an exercise intervention.

Chapter 3 presents the short-term (i.e., 12 weeks) effectiveness of HI and LMI exercise compared to a WLC group on cardiorespiratory fitness (peakVO₂), muscle strength (hand-grip strength and 30-second chair-stand test), and self-reported fatigue (Multidimensional Fatigue Inventory; MFI). Secondary outcomes included health-related quality of life (HRQoL), physical activity, daily functioning, mood and sleep disturbances, and body composition. Compared to the WLC group, both HI and LMI exercise interventions resulted in significant and clinically meaningful improvements in cardiorespiratory fitness, reductions in fatigue and improved HRQoL shortly after completion of primary cancer treatment. A potential dose-response relationship regarding exercise intensity was found for peakVO₂, favouring HI over LMI exercise. No significant intervention effects were found for hand-grip strength and the 30-second chair-stand test. HI and LMI exercise were equally beneficial in counteracting fatigue and physical function. Furthermore, compared to WLC, benefits in global quality of life and anxiety were found in the HI exercise, improved physical functioning in both the HI and LMI exercise, and less problems at work after LMI exercise.

Chapter 4 studied the hypothesis that a combined resistance and endurance exercise intervention improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and improving global quality of life (QoL) and physical function among cancer survivors who had completed curative treatment including chemotherapy. The results 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 cancer survivors' 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. 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 5 evaluated (a) the difference in cardiorespiratory fitness, muscle strength, fatigue, and HRQoL between HI and LMI exercise interventions at longer-term (i.e., 64 weeks after baseline); (b) changes in these outcomes between short-term to longer-term; and (c) the cost-effectiveness from a societal perspective. At longer-term follow-up, significant better

social and role function were found after HI exercise compared to LMI exercise. In addition, longer-term effects on global QoL and physical function were slightly better in HI than LMI exercise, but this was not statistically significant. Also, no significant differences between HI and LMI exercise were found for physical fitness and fatigue at longer-term follow-up. Furthermore, no significant changes between short- to longer-term follow-up were found in peakVO₂ and HRQoL in both HI and LMI exercise, indicating that intervention-induced benefits were successfully maintained at longer-term. However, fatigue returned to baseline values between week 12 and 64 in both groups. Cost-effectiveness analyses from a societal perspective showed that the probability that HI exercise was cost-effective compared to LMI exercise was 0.91 at €20,000/Quality-Adjusted Life Years (QALY) gained and 0.95 at €52,000/QALY gained, mostly due to significant lower healthcare costs in HI exercise.

Chapter 6 provides a comprehensive summary of previous studies on determinants of exercise intervention adherence and exercise maintenance after completion of an intervention in cancer survivors. Insight into the relevant and modifiable determinants of adherence is an important first step to improve intervention adherence. This literature review showed that exercise history is positively associated with exercise adherence. Other important demographic, clinical, psychosocial, physical, and environmental correlates of exercise adherence and maintenance could not be detected due to the limited number of studies and the inconsistency of findings across the studies. Moreover, the definition of exercise adherence varied across the included studies. Some studies exclusively focused on session attendance rate, while other studies also incorporated a measure on compliance. In conclusion, future studies are needed to further build the evidence for the influence of demographic, clinical, psychosocial, physical, and environmental factors on exercise adherence and maintenance. Additionally, it is recommended that future studies make a clear distinction between exercise attendance at supervised sessions and compliance to the prescribed type, time and intensity of exercises.

To further build the evidence on determinants of exercise intervention adherence, **Chapter 7** aimed to identify demographic, clinical, psychosocial, physical, and environmental factors associated with participation in and adherence to an exercise intervention among cancer survivors, using data from the REACT study. Results showed that cancer survivors with higher education, who were non-smokers, had lower psychological distress, higher outcome expectations, and who perceived more exercise barriers were more likely to participate in exercise interventions. These findings are worth acknowledging when promoting exercise

participation as part of cancer care. Furthermore, in HI exercise, participants with higher self-efficacy had higher session attendance rates, and higher compliance to the prescribed endurance exercises, and participants with lower psychological distress had higher compliance to the prescribed resistance exercises. In LMI exercise, non-smoking participants had higher compliance to resistance exercises, and participants with a higher body mass index had higher compliance to the prescribed resistance and endurance exercises. Additionally, breast cancer survivors had lower compliance with resistance and endurance exercises in LMI exercise than survivors of other types of cancer. These findings suggest that an individual's psychosocial factors, such as psychological distress and self-efficacy are important characteristics while performing HI exercise compared to LMI exercise. When offering a HI exercise intervention, we recommend to screen on these variables and if needed, include behavioral motivational strategies to improve compliance or consider starting at a lower training intensity.

Given the beneficial effects of physical activity on health outcomes among cancer survivors, effective interventions to obtain and maintain sufficient levels of physical activity are warranted. In **Chapter 8** we explored demographic, clinical, psychosocial, and environmental correlates of physical activity among from 574 female breast cancer survivors who had participated in three different intervention studies: REACT, Exercise and Nutrition Routine Improving Cancer Health (ENRICH), or Move More for Life (MM4L). Results indicated that female breast cancer survivors who were older, had a higher body mass index, lower self-efficacy, or less social support from family and friends may be at higher risk of being physically inactive. Therefore, future interventions to promote physical activity among breast cancer survivors should specifically target patients who are older, and have a higher body mass index, and operationalize behavior change strategies designed to enhance self-efficacy and social support.

In **Chapter 9** the main findings of the studies were presented and interpreted. Furthermore, the methodological considerations including study population, participation rates and generalizability of the results, study designs and statistical power and the choice of outcome measures were discussed. Overall, this thesis advocates the implementation of exercise interventions as part of standard cancer care for cancer survivors, because results showed that exercise interventions can improve cardiorespiratory fitness, reduce fatigue and enhance HRQoL in cancer survivors shortly after completion of cancer treatment. HI exercise may be preferred over LMI exercise when aiming to improve peakVO₂ and HRQoL,

because it may yield larger effects. Moreover, HI exercise was cost-effective in terms of QALY compared to LMI exercise. In the final part of the chapter, future research suggestions were presented. Additional research should further disentangle the effects of different exercise frequency, intensity, type and time (i.e., FITT factors) among different subgroups of patients to optimize evidence-based exercise recommendations for cancer survivors. Furthermore, future studies should focus on identifying intervention moderators explaining 'for whom' or 'when' interventions are most effective? Finally, more insight into the working mechanisms of exercise interventions (i.e., mediators) on health outcomes in cancer survivors is needed to improve the efficacy and efficiency of interventions.