

## Chapter 7

# Summary, general discussion and perspectives



## INTRODUCTION

Although survival rates in childhood cancer have improved, the prevention and reduction of late effects remain an important goal. Therefore, nowadays, research also focuses on the development of effective (preventive) interventions to enhance physical and/or psychosocial functioning of childhood cancer patients or survivors. To our knowledge, there are, to date, no rehabilitation programs for childhood cancer patients that combine both physical and psychosocial training for childhood cancer patients.

This thesis reports on the effects of a combined physical and psychosocial intervention for childhood cancer patients (aged 8-18 years), that aims to enhance both their physical and psychosocial functioning.

This final chapter summarizes the results of the work reported in this thesis, discusses the strengths and limitations of the study, suggests directions for future research, and presents some clinical implications related to the findings.

## SUMMARY

**Chapter 2** describes the design and methodology of our multicenter randomized controlled trial. In this trial, a 12-week combined physical and psychosocial training intervention was offered to childhood cancer patients (aged 8-18 years) during their treatment, or within the first year after the end of treatment. Childhood cancer patients may benefit from such a combined intervention as it may help maintain or enhance their physical fitness and increase their quality of life. However, the patients' needs for such an intervention, and the applicability and effectiveness of the intervention need to be established before implementation of such an intervention as part of standard clinical care.

The aim of the study presented in **Chapter 3** was to examine the factors that influence the choice of childhood cancer patients' to participate (or not) in the combined intervention. Of the 174 eligible patients, only 40% decided to participate in the study. This relatively low participation rate raised questions about willingness to participate in the study, because decreased physical fitness is a common problem in this population and therefore it was expected that rates

would have been higher. The non-participants were, therefore, asked to fill in a one-time questionnaire about their reasons for not participating in the study, and to provide details about their physical activity, health-related quality of life (HrQoL) and behavioral problems; the study-participants also completed the same questionnaire at baseline. Of the non-participants, 61 (57.5%) completed the one-time survey. It appeared that the main reasons for non-participation were the time-consuming nature and burdensomeness of the intervention. Also, a greater distance between home and hospital was negatively related to participation. No differences were found between participants and non-participants regarding age, HrQoL, parental-reported behavior problems, sports participation, type of school, body mass index, and perceived health. In general, non-participants rated their fitness level as higher compared with that of the participants. Patients with more (internalising) behavioral problems appeared more likely to participate in the study. So we cautiously conclude that we seem to have reached those young people that are probably in most need of such an intervention.

Since the psychosocial part of the intervention was not pilot tested before the randomized controlled trial started, **Chapter 4** presents an explorative study to assess the applicability of this individualized structured psychosocial intervention to enhance social-emotional functioning and coping with disease-related effects in childhood cancer patients. The program included six sessions for children and two sessions for parents. The content of the program covered psycho-education and cognitive-behavioral techniques that are applied to enhance awareness of feelings, thoughts and behavior (as well as their consequences), and to reinforce coping strategies. Questionnaires were used to evaluate completion of the psychosocial intervention, coping and satisfaction with the psychosocial intervention by patients and psychologists, and ranking of the individual topics by patients, parents and psychologists. Of the 30 patients [mean age 13.0 (SD 3.0) years; 53.3% male; 30% still on treatment] who participated in the psychosocial intervention, two dropped-out due to medical complications and one due to lack of time; thus, 90% completed the psychosocial intervention. Overall, patients appreciated their participation in the intervention and were positive about the psychologists. The psychologists themselves were also satisfied with several aspects of the intervention. Minor adaptations were suggested by both patients and psychologists, including customizing the intervention according to age, and applying a more patient-tailored approach. Patients, parents



and psychologists indicated that the expression of feelings was a highly important topic of the intervention. Another topic, implicated as important, was enhancing self-perception. Parents attached more value to coping skills than the patients themselves and their psychologists. On the other hand, patients attached more value to discussing changes in the family than parents and the psychologists. Based on the good adherence rate, and also because patients and psychologists reported to be satisfied with the intervention, we conclude that the psychosocial intervention appears to be applicable for childhood cancer patients during treatment, or shortly thereafter.

**Chapter 5** examined the effect of the QLIM intervention on psychosocial functioning and HrQoL. Assessment of HrQoL, depressive symptoms, behavior problems and self-esteem (by questionnaires) took place at baseline, after 4 months (shortly after the end of the intervention period) and again at 12 months post-baseline. Overall, the intervention showed no positive benefits for HrQoL and psychosocial functioning, with the exception of a modest effect on the presence of pain, although this was based on the parents' perspective only. No effects were found based on the patients' self-report.

**Chapter 6** describes the short and long-term effects of the intervention on the primary study outcome physical fitness (cardiorespiratory fitness and muscle strength) as well as on the secondary physical outcomes. Subsequently, the potential mediating effect of changes in physical or psychological functioning on HrQoL was investigated. The long-term assessment revealed a significant beneficial effect of the intervention on lower body muscle strength, whereas no effects on physical outcomes were found directly after the intervention. No significant mediating factors were found in this study. The physical training seemed to be applicable and had reasonably good adherence rates. Based on the results from Chapters 5 and 6 we conclude that, in its current form, this combined intervention shows only limited positive effects and should not yet be implemented as part of standard clinical care.

## STRENGTHS AND LIMITATIONS

To our knowledge, the QLIM study is the first randomized controlled trial to evaluate the effects of a combined physical and psychosocial training intervention for

childhood cancer patients. All cancer patients (aged 8-18 years), who were still on treatment or within the first year after the end of treatment, were given the opportunity to participate, irrespective of their diagnosis. This resulted in a relatively heterogeneous group, whilst most other intervention studies focused on one diagnosis only (e.g. ALL [1-5], or brain tumors [6-7]). Although we aimed to include 100 participants in our study, the participation rate (40%) proved to be lower than we expected. Therefore, we decided to include two additional pediatric oncology centers and extended the inclusion period by one year. Recruitment was eventually stopped with 68 participants available at the baseline measurement (for which a minimum of 60 participants was required based on an expected 20% greater improvement on cardiorespiratory fitness, the primary outcome of the total study, in the intervention group). Although it took longer than expected to recruit a sufficient number of participants, analyses of the included participants revealed that we seemed to have reached those patients in need of physical and/or psychosocial training. This conclusion was based on the lower appraisal of their physical fitness and their higher level of internalizing problems compared to the non-participants.

As mentioned earlier, studying the short- and long-term effects of the combined physical and psychosocial training intervention showed limited effects of the intervention: at long-term follow-up, the intervention group showed a greater improvement on lower body muscle strength and pain-related HrQoL from a parents' perspective, compared to the 'care as usual' control group. The lack of other significant effects of the intervention, especially on the primary outcome cardiorespiratory fitness, was unexpected. Nevertheless, from this trial we learned that it is possible to implement such a demanding intervention for children and their parents, who were already heavily burdened by the disease and treatment period itself. Both the physical and psychosocial training intervention seemed to be applicable and the patients reported to be satisfied with both parts of the combined intervention. This is very promising for future intervention studies, bearing in mind that such interventions need to become more effective.

Some limitations of our study need to be addressed. First, on long-term follow-up the minimum number of participants required in each study arm was no longer available; this was mainly due to the recurrence of the disease in both groups and the subsequent dropout. This led to relatively small groups which did not allow for subgroup analyses, e.g. analysis by diagnosis, or number of children with/without



problems in the clinical range. Therefore, we cannot provide specific information about which children are more likely to benefit from the intervention than others. Secondly, for this study the power calculations were based on improvements in cardiorespiratory fitness and not on psychosocial outcomes. We probably required more participants in each group to detect more relevant differences between the intervention and control group regarding the psychosocial outcomes. Post-hoc power analysis showed that at least 165 patients had to be included in the study to detect differences between the intervention and control group on parent-reported HrQoL. In retrospect, the power calculations should have been performed on psychosocial outcome measures and on the other physical outcome measures; this would have provided more adequate numbers of participants in each study arm to detect differences between the groups and allow subgroup analyses to detect certain risk groups. For example, we could not compare the results of participants with and without clinically significant problems due to the small numbers of participants with questionnaire scores in the clinical range. At baseline, 10% of the children aged under 12 years and 23% of the adolescents in our study group, rated their HrQoL as being more than 2 standard deviations below the norm of healthy Dutch children. Also, 13% of the adolescents reported clinically significant internalizing behavior and, of all participants, only 7% reported depressive symptoms. Therefore, we have to bear in mind that the psychosocial functioning of most participants was generally in the normal range at baseline. This raises the question as to whether we should have expected any significant intervention effects at all. To reach sufficient numbers of participants to perform subgroup analyses, and to detect more potential differences between both groups, a nationwide study and/or a longer inclusion period is necessary; this conclusion is based on the considerable efforts required in the present study to recruit sufficient numbers of participants, which eventually resulted in only 68 participants. Third, the number of participants in each study group was skewed due to the four-factor stratification rules. Fourth, a threefold-bias problem needs to be addressed. In the comparison between non-participants and participants we were only able to include just over 50% of all non-participants in the analyses. Therefore, the group of non-participants could be biased and not entirely representative for the entire group of non-participants. Another consideration is that the participants might have had a more positive attitude towards accepting physical and psychosocial training, due to the lower appraisal of their physical fitness and their higher level of internalizing problems compared to non-participants. In the 'care as usual' control group the patients

were free to choose whatever support they needed and they might have had a heightened interest in physical and/or psychosocial support. In addition, the importance of physical and psychosocial training was also emphasized in the written study information. The third bias problem might be related to the patients' evaluation of the psychosocial training as good. Because the intervention placed high demands on patients, and much time and effort was required for the intervention, this might have encouraged the participants to emphasize the importance of the intervention in order to justify (or at least not to contradict) their 'personal investment'.

## DIRECTIONS FOR FUTURE RESEARCH

Only a few studies are available on the effectiveness of psychosocial interventions and, so far, they have shown limited beneficial effects for the patients themselves [1-2]. The few studies on the effects of physical training for children with childhood cancer also showed minimal effects [3-7]. However, it is suggested that these limited effects were due to small study populations and/or to a less than optimal study design [3]. In the randomized controlled trial presented in this thesis, we tried to overcome these methodological issues; nevertheless, we also found only limited effects. This result does not seem to match the general intuitive opinion of physicians that physical training must have some beneficial effect. Future research needs to explore other training methods, i.e. physical, psychosocial and the two combined.

The timing of the intervention also needs to be considered. Offering the training at an earlier stage than in the present study (i.e. perhaps during the most intensive phase of cancer treatment) might prevent a further decline in physical fitness and psychosocial functioning. In the study of Hartman et al. [5], physical training for ALL patients started directly after diagnosis. The authors also found no significant effect of the training, but the physical intervention in their study was different from ours. The intervention of Hartman et al. [5] was mainly home-based/not supervised and was hospital-based only once every six weeks (thus less intensive than our physical intervention). From a psychosocial perspective most patients function relatively well during their treatment [10-12] and, although ratings of HrQoL are impaired shortly after diagnosis, most children rate their HrQoL at the end of treatment as being similar to that of healthy children [13]. This seems to

suggest that natural recovery takes place. If this is the case, then it might be better to offer the training (both physical and psychosocial) at a later time, i.e. after this period of natural recovery. Children in this stage might be more capable to perform intensive training which, in turn, might increase the training effect. A small pilot study performed by Takken et al. [7] found no significant training effects when an intensive physical intervention was offered at least six months after the end of treatment. However, that study included only nine patients and, because it was considered too demanding, there was a high dropout rate. Therefore, the physical intervention used in that earlier study [7] was adapted for the present QLIM study; moreover, a psychosocial intervention was added to increase acceptability and to gain a more significant training effect. Although this effect was not achieved, the present intervention was less demanding, as shown by the good adherence rates for both the physical and psychosocial training; i.e. after excluding the dropouts ( $n=15$ ; 22% mainly due to medical complications/recurrence of disease), 77% of the participants completed all physical training sessions and 100% completed all psychosocial sessions.

In the present research, we wanted all childhood cancer patients to have the opportunity to participate in our study; this resulted in a heterogeneous group. Therefore future studies could look for specific risk factors for lower physical (and psychosocial) functioning, e.g. by diagnosis, treatment modality, and physical and/or psychosocial functioning before diagnosis. In our group, the psychosocial functioning was generally in the normal range at baseline; this limited the possibility to find certain risk groups that might benefit the most from the intervention. In the case that risk factors can be assessed, screening for this must be accounted for and the adapted intervention should only be offered to those in need of such an intervention, as based on objective measures (and not based on self-report alone). A challenge for research on risk factors is to recruit a sufficiently large study population to allow to perform subgroup analyses.

To enhance the participation rate in future 'demanding' studies, focus groups could be formed to examine potential barriers and motivators to participate in this type of study. For the psychosocial intervention, more convenient ways to offer this intervention should be explored. Training psychologists in a primary healthcare setting closer to the home, to offer such an intervention to childhood cancer patients and survivors is an option. However, these psychologists are not likely to be specialized in childhood psycho-oncology and this could limit the



effectiveness of the intervention. Another option which is more in line with recent research [14-15] is to consider adapting the psychosocial intervention to an online version.

## CLINICAL IMPLICATIONS

Based on the limited positive benefits that we observed from our combined physical and psychosocial intervention, we can conclude that the present intervention should not be offered as part of standard clinical care; more research is required. However, the present study illustrates that implementing a combined physical-psychosocial intervention is feasible with only a limited number of dropouts and with good adherence rates. This is promising for the development of new interventions in the future.

## FINAL CONCLUSION

From the psychological perspective we conclude that, in contrast to expectations, the combined physical and psychosocial intervention for childhood cancer patients during and after their treatment did not enhance their HrQoL and/or psychosocial functioning, with the exception of pain-related HrQoL from the parent's perspective. The intervention did show significant beneficial long-term effects for lower body strength, i.e. children in the intervention group gained more strength in their hips, knees and ankles compared to children in the control group. However, no effect was found on the primary outcome of our study, i.e. cardiorespiratory fitness. Since the effects of this intervention were limited, this intervention should not yet be implemented as part of standard clinical care for the time being.

Nevertheless, the present study has shown that, although reaching only 40% of all eligible patients, implementing and organizing such a demanding intervention is possible for a considerable proportion of patients and that good adherence rates and positive evaluations by these patients can be achieved. Therefore, it is worthwhile to examine other possible interventions that might enhance the physical and/or psychosocial functioning of childhood cancer patients and survivors.



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