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Maurice-Stam, H.; Oort, F.J.; Last, B.F.; Brons, P.P.; Caron, H.N.; Grootenhuis, M.A.

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Original article

School-aged children after the end of successful treatment of non-central nervous system cancer: longitudinal assessment of health-related quality of life, anxiety and coping

H. MAURICE-STAM, PHD, *Psychosocial Department, Emma Kinderziekenhuis Academic Medical Center, University of Amsterdam, Amsterdam*, F.J. OORT, PHD, *Department of Medical Psychology, Academic Medical Center, Amsterdam, Department of Education, Faculty of Social and Behavioural Sciences, University of Amsterdam, Amsterdam*, B.F. LAST, PHD, *Psychosocial Department, Emma Kinderziekenhuis Academic Medical Center, University of Amsterdam, Amsterdam, Department of Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam*, P.P.T. BRONS, MD PHD, *Radboud University Nijmegen Medical Center, Nijmegen*, H.N. CARON, MD, PHD, *Department of Paediatric Oncology, Emma Kinderziekenhuis Academic Medical Center, University of Amsterdam, Amsterdam*, & M.A. GROOTENHUIS, PHD, *Psychosocial Department, Emma Kinderziekenhuis Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands*

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School-aged children after the end of successful treatment of non-central nervous system cancer: longitudinal assessment of health-related quality of life, anxiety and coping

The aim of the study was to investigate: (1) health-related quality of life (HRQoL) and anxiety in school-aged cancer survivors during the first 4 years of continuous remission after the end of treatment; and (2) correlations of disease-related coping with HRQoL and anxiety. A total of 76 survivors aged 8–15 years completed questionnaires about HRQoL, anxiety and disease-related cognitive coping at one to five measurement occasions. Their HRQoL was compared with norm data, 2 months ($n = 49$) and 1 year ($n = 41$), 2 years ($n = 41$), 3 years ($n = 42$) and 4 years ($n = 27$) after treatment. Through longitudinal mixed models analyses it was investigated to what extent disease-related cognitive coping was associated with HRQoL and anxiety over time, independent of the impact of demographic and medical variables. Survivors reported worse Motor Functioning (HRQoL) 2 months after the end of treatment, but from 1 year after treatment they did no longer differ from the norm population. Lower levels of anxiety were associated with male gender, being more optimistic about the further course of the disease (predictive control) and less searching for information about the disease (interpretative control). Stronger reliance on the physician (vicarious control) was associated with better mental HRQoL. As a group, survivors regained good HRQoL from 1 year after treatment. Monitoring and screening survivors are necessary to be able to trace the survivors at risk of worse HRQoL.

Keywords: anxiety, coping, paediatric oncology, quality of life.

Correspondence address: Heleen Maurice-Stam, Psychosociale afdeling, Emma kinderziekenhuis AMC, G8-224, Meibergdreef 9, NL-1105 AZ Amsterdam, the Netherlands (e-mail: h.stam@amc.uva.nl).

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INTRODUCTION

The treatment of patients with childhood cancer has enormously improved in recent decades. Many patients who may previously have had a limited life expectancy are now growing up with childhood cancer and surviving into adulthood. The overall 5-year survival rate for children diagnosed with cancer in Europe is currently more than 70% compared with 30% in the 1960s (Stiller *et al*. 2005; Magnani *et al*. 2006).

The diagnosis and treatment of childhood cancer is a dramatic event that affects the daily life and emotional well-being of all family members (Eiser 2004). An increasing number of studies have been directed at assessing health-related quality of life (HRQoL) and emotional adjustment in long-term survivors of childhood cancer. Less is known about the first few years after treatment in the run-up to long-term survivorship, and longitudinal studies are sparse. Sawyer *et al.* (2000) found that patients had behavioural–emotional problems immediately after diagnosis, but in the next 4 years the scores were generally consistent with those in the control group. Others (Kazak *et al*. 1994; Radcliffe *et al*. 1996; Grootenhuis & Last 2001) reported that survivors did not show elevated levels of anxiety in comparison with the norm in the first years after termination of treatment. Recently, we found that 2 months after the end of successful cancer treatment, paediatric patients and their parents experienced worse HRQoL than the general population did, to a clinically relevant extent (Stam *et al*. 2006).

Demographic and medical factors related to the HRQoL and emotional functioning of paediatric survivors have been discussed to some extent in many studies. The results, however, were not consistent, and most study designs were cross-sectional so that causality can not be established. What can be concluded is that older age at diagnosis, longer time off treatment, irradiation therapy and severe medical late effects were associated with worse psychosocial functioning in paediatric long-term survivors of childhood cancer [see review of Stam *et al*. (2001)].

The role of coping is important in relation to the adjustment to childhood cancer (Last & Grootenhuis 1998). Coping consists of actions, behaviours and thoughts aimed at dealing with the demands of events and situations that are appraised as stressful (Lazarus & Folkman 1984). So, coping mediates the effect of a stressor on an individual's well-being. In the context of coping with a life-threatening illness the following disease-related cognitive control strategies were found to be relevant (Grootenhuis *et al*. 1996). *Predictive control* means that patients attempt to predict events in order to create the feeling that they are able to control the situation. Having positive expectations helps patients to deal with the consequences of disease. *Vicarious control* strategies concern the attribution of special power to others in the case of cancer patients to the doctors, on whom they are dependent, and all hope is focused. Because one can not alter the course of the disease, belief in powerful others can be adaptive. *Interpretative control* refers to the search for meaning and understanding. Using information to help to understand emotional reactions or to reduce uncertainty is interpretative control strategies. Finally, with *illusory control* one attempts to associate with chance, such as hoping for a miracle or wishful thinking.

Some studies on coping strategies in paediatric survivors of cancer were found. Madan-Swain *et al*. (1994) found that, overall, survivors used coping strategies which were comparable with the strategies used by controls. Others found that survivors tended to apply more avoidance strategies in stressful situations than a healthy control group (Bauld *et al*. 1998), which is in line with the coping strategies found in paediatric cancer patients during treatment (Phipps *et al*. 2001; Landolt *et al*. 2002). It is difficult, however, to conclude whether coping is associated with the patient's functioning because most studies have been focused on coping as an outcome variable, rather than a predictor. Moreover, the few studies on the impact of coping on survivors' functioning showed inconsistent results (Phipps *et al*. 2001).

The more we understand about disease-related coping and about the relation of coping with survivors' functioning, the better healthcare providers will be able to help patients to live with the consequences of their disease. The present study was therefore directed at HRQoL and emotional functioning as well as disease-related coping. A longitudinal study was designed among 76 school-aged survivors with the following research questions: (1) How are the course of HRQoL and anxiety of survivors during the first 4 years of continuous remission following the completion of treatment for cancer? and (2) To what extent is disease-related cognitive coping associated with survivors' HRQoL and anxiety during the first 4 years of continuous remission following the completion of treatment for cancer? Although a 5-year period without treatment is commonly considered a criterion of survival, we decided to call the patients in our study 'survivors' because they were in continuous remission in the run-up to long-term survivorship.

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MATERIAL AND METHODS

Procedure

The results presented here are taken from a Dutch study on the late psychosocial consequences of cancer in childhood, which started in 2000 and ended in 2006, the Vragenlijsten KinderOncologie Latere Gevolgen (VOLG; Questionnaire on childhood cancer late questionnaire) study. From 2000 to 2002, survivors and their parents were recruited from two Dutch university hospitals, the Emma Children's Hospital at the Academic Medical Center in Amsterdam and the Radboud University Nijmegen Medical Center. The Medical Ethics Committees of the hospitals have approved the study protocol.

All consecutive survivors who met the inclusion criteria during these periods were invited to participate in the VOLG study. The inclusion criteria were: (1) age 1–18 years; (2) complete remission; (3) end of successful treatment at most 2 months before; and (4) ability to complete Dutch questionnaires. The self-reported data of survivors aged 8–15 years ('school-aged survivors') were used in the present study. This means that the data were included in the analyses at the measurement occasions that the respondent was aged 8–15 years.

Once informed consent had been obtained from both the survivors and their parents, the respondents completed several questionnaires, 4–6 times, depending on the year of inclusion. The first five assessments were used for analyses: approximately 2 months (M1), 1 year (M2), 2 years (M3), 3 years (M4) and 4 years (M5) after the end of treatment. Data of the sixth measurement occasion and data for survivors with central nervous system (CNS) tumours were not used because of too small numbers of respondents. Furthermore, the data for patients who relapsed were excluded from analysis from the moment of the relapse.

MEASURES

Dependent variables: HRQoL and anxiety

The *TNO-AZL Children's Quality of Life Questionnaire* (TACQOL) for children aged 8–15 years (Verrips *et al*. 1999; Vogels *et al*. 2004a,b) was used. This is a generic Dutch instrument that measures HRQoL on group level in a reliable and valid way. Norm data from the general Dutch population are available (Verrips *et al*. 1998, 1999; Vogels *et al*. 1998). The questionnaire measures health status problems weighed by the impact of the problems on well-being. Most of the items consist of two questions linked to one another. The first one is about the frequency of the problem in the past few weeks. The second one rates the possible negative emotional responses to the problems on a 4-point Likert scale. The items are clustered into seven multi-item scales with higher scores indicating better HRQoL: Physical Complaints, Motor Functioning, Autonomy, Cognitive Functioning, Social Functioning, Positive Emotions and Negative Emotions. Following the method of Ware & Kosinski (2001) we used Principal Component Analysis (PCA) to aggregate all TACQOL scale scores into two summary scales: the Mental Component Scale (MCS) and the Physical Component Scale (PCS). The relative contribution of each scale to MCS and PCS was derived from PCA at M1, oblique rotation (Oblimin).

Anxiety was measured with the Dutch version of the *State-Trait Inventory for Children*, the ZBV-K (Bakker *et al*. 1989). The 'trait' version was used to assess the tendency to respond with anxiety in a stressful situation. This version is more appropriate to measure the overall level of anxiety a child experiences than the 'state' version that measures conditional anxiety at the very moment of assessment. Higher scores indicate higher levels of anxiety. The norm data from the general Dutch population of school-aged children (Bakker *et al*. 1989) could not be used because only gender-specific norm data were available, which resulted into too small subgroups of survivors at the several measurement occasions.

Independent variables: disease-related cognitive control and medical variables

Disease-related cognitive coping was assessed with the *Cognitive Control Strategies Scale* (CCSS) for patients. The instrument, based on the model of Rothbaum *et al*. (1982), was developed at the Psychosocial Department of the Emma Children's Hospital/AMC. It assesses to what extent respondents try to gain sense of control over the illness by using cognitive coping strategies, measured on a 4-point Likert scale. Higher scores represent a stronger reliance upon the control strategy. The questionnaire proved to be reliable and useful in earlier studies (Grootenhuis & Last 2001; Loonen *et al*. 2002; Stam *et al*. 2006). The items of the CCSS-CF were grouped into four scales, as described in *Introduction*: predictive, vicarious, interpretative and illusory control. The Illusory Control Scale was not used in analyses because of insufficient internal consistency.

Medical data were obtained from the survivor's medical record. The prognosis was based on the survival chances at diagnosis as rated by each survivor's oncologist, namely <25%, 25–75% or >75%. After the end of treatment (M1), the parents were asked to rate their perception of the intensiveness of their child's treatment on a Visual Analogue Scale, from 'totally non-intensive' (0, left end of line)

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to 'very intensive' (10, right end of line). They were also asked to assess the visible consequences of the disease. Their answers were dichotomized to 'presence' or 'absence' of visible consequences.

Statistical analyses

SPSS version 12.0 was used for all analyses. Survivors' HRQoL over time was compared with norm data for the general Dutch population of children aged 8–11 years and 12–15 years, with respect to the four TACQOL scales with sufficient internal consistency at each measurement occasion: Motor Functioning, Cognitive Functioning, Positive Emotions and Negative Emotions. One sample *t*-tests or non-parametric equivalents (one sample sign-test or binomial test) were performed to test (at $P < 0.05$, two-sided) whether the mean score, the median or the binomial distribution of the scales scores in the childhood cancer survivors differed from that in the norm population.

Linear mixed model analysis (Snijders & Bosker 2004) was performed to examine the course of HRQoL and anxiety, and to explore to what extent disease-related cognitive coping was predictive of HRQoL (PCS and MCS) and anxiety, while controlling for demographic and medical variables. To account of repeated measures within respondents, linear mixed models were fitted to the data. These models can also be characterized as multi-level models for longitudinal data, with measurement occasions as first level units of analysis and respondents as second level units. The major advantage of linear mixed model analysis is that all available data are incorporated into the analysis, including data from survivors who missed one or more measurement occasions. Changes in the numbers of subjects from occasion to occasion do not harm the analysis, other than that the statistical power to find deviations from baseline decreases with higher attrition.

To facilitate interpretation of regression coefficients, all continuous scores were transformed into standard normal scores, expressing deviations from the mean at M1. We considered standardized regression coefficients of 0.1 as small, 0.3 as medium and 0.5 as large after Cohen (1988). For binary coded predictor variables, regression coefficients of 0.2 can be considered small, 0.5 medium and 0.8 large.

Measurement occasions were treated as fixed because growth-curve models were not appropriate for these data. The intercept was considered random with its mean equal to the standardized mean outcome at M1, thus taking the outcome at M1 as reference point. In this way, parameter estimates for M2 through M5 can be interpreted as deviations from baseline (M1). The deviations were treated as fixed parameters after checking for random parameters, using Akaike's information criterion.

Models were fitted for PCS, MCS and anxiety. Because of the large number of predictor variables in relation to the sample size, pre-selection was necessary. The initial model consisted of the random intercept (M1) and the fixed parameters for measurement occasions M2 to M5. Demographic and medical predictor variables were entered one by one into the initial model. If significant at least at 0.3, the demographic and medical variables were selected for the final model. All three variables concerning cognitive coping were included. The final model thus consisted of the random intercept (M1), the fixed regression coefficients for M2 through M5 and the three coping variables, completed with the demographic and medical predictor variables that remained after pre-selection. For one outcome anxiety, there appeared to be no intercept variance. The final model for this outcome was therefore fitted with a fixed intercept. Percentages of total explained variance were calculated.

For each model, we checked whether the longitudinal covariance structure was best described by compound symmetry or by an autoregressive structure, with reference to Akaike's information criterion. Compound symmetry appeared to give the best fit for all models. Furthermore, we checked whether first-order interaction effects of measurement occasion with the other predictor variables should be added to the model. To prevent too many findings occurring by chance, these tests were carried out at Bonferroni adjusted level of significance. We concluded that it was not necessary to add any of the first-order interaction effects.

RESULTS

Participants

A total of 164 consecutive survivors whose cancer treatment had successfully ended, were invited to participate in the longitudinal part of the VOLG study. The response rate was 81.7% ($n = 134$). The 30 families who did not participate did not differ from participating families with respect to demographic and medical variables ($P < 0.1$ at *t*-tests or χ^2-tests).

A total of 76 survivors that were included in the present study were aged 8–15 years at one or more measurement occasions: 49 survivors at M1, 41 at M2, 41 at M3, 42 at M4 and 27 at M5. Characteristics of survivors are presented in Table 1. Dropout because of non-response was 2.6% ($n = 2$). Furthermore, after recurrence of the childhood cancer, data of subsequent measurement occasions were excluded from analyses ($n = 8$, 10.5%). So, it depends on the moment of

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Table 1. Characteristics of the survivors

Measurement: time since end of treatment	M1 2 months	M2 1 year	M3 2 years	M4 3 years	M5 4 years
n	49	41	41	42	27
Gender (female): *n* (%)	17 (34.7)	15 (36.6)	13 (31.7)	15 (35.7)	5 (18.5)
Age (range at M1: 8.1–15.9): mean (standard deviation)	12.1 (2.3)	11.8 (2.5)	11.5 (2.5)	11.5 (2.4)	10.9 (2.2)*
Age category: *n* (%)					
8–11 years	23 (46.9)	19 (46.3)	25 (61.0)	25 (59.5)	21 (77.8)
12–15 years	26 (53.1)	22 (53.7)	16 (39.0)	17 (40.5)	6 (22.2)
Age at diagnosis (range at M1: 6.4–15.2): mean (standard deviation)	11.0 (2.4)	9.9 (2.5)*	8.6 (2.6)*	7.5 (2.7)*	5.7 (2.4)*
Time since diagnosis (months) (range at M1: 2.0–28.0): mean (standard deviation)	13.2 (7.2)	23.7 (7.1)	35.2 (7.9)	48.3 (8.9)	62.4 (10.4)
Duration of treatment (months) (range at M1: 1.2–25.7): mean (standard deviation)	10.9 (7.3)	10.7 (6.9)	10.9 (7.7)	12.1 (8.6)	14.3 (10.3)
Diagnosis: *n* (%)					
Leukaemia/lymphoma					
Solid tumour	24 (49.0)	18 (43.9)	20 (48.8)	22 (52.4)	20 (74.1)
Treatment: *n* (%)	25 (51.0)	23 (56.1)	21 (51.2)	20 (47.6)	7 (25.9)
Chemotherapy	48 (98.0)	41 (100)	41 (100)	42 (100)	27 (100)
Radiotherapy	8 (16.3)	6 (14.6)	4 (9.8)	4 (9.5)	0*
Surgery	21 (42.9)	21 (51.2)	20 (48.8)	20 (47.6)	10 (37.0)
Autologous bone marrow transplantation	0	0	0	0	0
Other	1 (2.0)	0	0	0	0
Prognosis at diagnosis: *n* (%)					
<25%	1 (2.0)	0	0	0	0
25–75%	21 (42.9)	15 (36.6)	13 (31.7)	11 (26.2)	5 (18.5)
>75%	27 (55.1)	26 (63.4)	28 (68.3)	31 (73.8)	22 (81.5)*
Native country (the Netherlands): *n* (%)	48 (98.0)	41 (100)	40 (97.6)	41 (97.6)	26 (96.3)

*Survivors differed significantly from the survivors at M1, $P < 0.05$ (two-sided).

relapse how many measurement occasions were included. Data at M5 were not available in 19 (25.0%) survivors because of the finite follow-up period of the VOLG study. The survivors included at M2, M3, M4 and M5 did not differ significantly ($P < 0.05$) from the survivors at M1 with respect to their demographic and medical characteristics, except for age at diagnosis. The survivors at M1 were older at diagnosis than the survivors at the other measurement occasions. Furthermore, some differences were found between survivors at M5 and those at M1, as shown in Table 1. Finally, participants did not differ from the non-participants at the several measurement occasions with respect to their outcome scores at T1.

Health-related quality of life and anxiety over time

On average 2 months after the end of successful treatment (M1), survivors aged 8–11 years scored significantly worse on Motor Functioning ($P < 0.05$) than the general Dutch population: M = 27.7 (standard deviation = 4.6) vs. M = 29.8 (standard deviation = 3.2). At M1, also survivors aged 12–15 years reported significantly worse Motor Functioning ($P < 0.001$) than the general Dutch population: M = 24.8 (standard deviation = 5.4) vs. M = 29.8 (standard deviation = 3.3). The differences were large, d = –0.7 and d = –1.6 respectively. One (M2), two (M3), three (M4) and four years (M5) after the end of treatment, survivor's level of Motor Functioning was normalized in both aged groups. The survivors aged neither 8–11 nor 12–15 years differed from the general population with respect to Cognitive Functioning, Positive Emotions and Negative Emotions at any measurement occasion (Fig. 1a and b).

Predictors of HRQoL

Parameter estimates from the longitudinal mixed models analyses of survivor's HRQoL are shown in Table 2. Survivors reported significant higher scores on PCS 1–4 years after the end of treatment than at 2 months. The effects of time were small to medium. Principal Component Analysis was not predicted significantly ($P < 0.05$) by any demographic, medical or coping variable. Interpretative control, however, was associated negatively with PCS at $P = 0.08$ ($\beta = -0.10$).

MCS, in contrast with PCS, was not associated significantly ($P < 0.05$) with measurement occasion, although at

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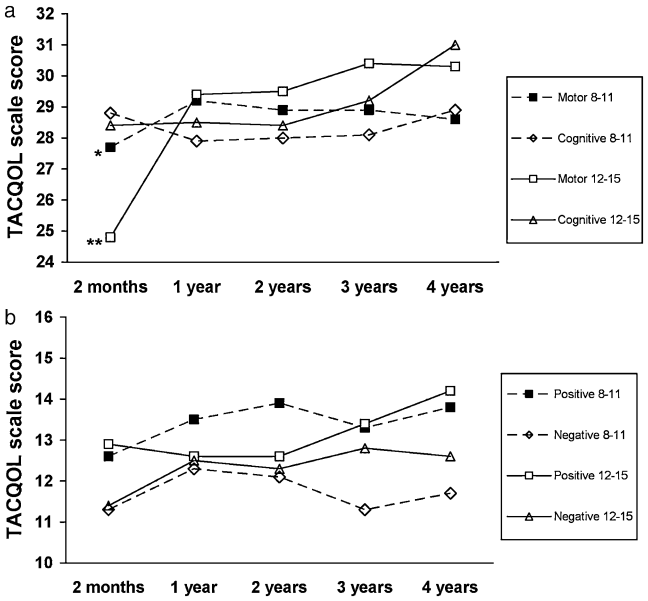

Figure 1. Health-related quality of life (HRQoL) in survivors aged 8–11 and 12–15 years over measurement occasions: mean TNO-AZL Children's Quality of Life questionnaire (TACQOL) scale scores† compared with the norm‡.
*Scale score differed significantly from the norm at $P < 0.05$ (two-sided) at one sample *t*-test; **Scale score differed significantly from the norm at $P < 0.001$ (two-sided) at one sample *t*-test.
†Higher scores represent better HRQoL: Range Motor and Cognitive Functioning = 0–32, Range Positive and Negative feelings = 0–16.
‡General Dutch population of children aged 8–11 years (Vogels *et al*. 2004b) and 12–15 years (Vogels *et al*. 2004a).

M2 and M3 survivors tended to report better MCS than at the first measurement occasion: $\beta = 0.36$, $P = 0.06$ and $\beta = 0.54$, $P = 0.08$ respectively. Furthermore, a small positive effect was found for vicarious control ($\beta = 0.13$, $P < 0.05$). Good prognosis tended to be associated negatively with MCS ($\beta = -0.35$, $P = 0.07$), as did interpretative control ($\beta = -0.13$, $P = 0.053$).

Predictors of anxiety

Parameter estimates from the longitudinal mixed models analyses of survivor's level of anxiety are shown in Table 3. Measurement occasion did not contribute significantly to the model, where gender and coping were associated significantly with anxiety. The female reported higher levels of anxiety than the male ($\beta = 0.60$, $P < 0.001$), which was a medium to large effect. Higher scores on predictive control were associated with lower levels of anxiety ($\beta = -0.18$, $P < 0.05$), but higher scores on interpretative control were associated with higher levels of anxiety ($\beta = 0.18$, $P < 0.05$). The effects of cognitive coping were small to medium. Finally, survivors who were treated with chemotherapy without radiotherapy tended to report a higher level of anxiety ($\beta = 0.51$, $P = 0.08$) than the other survivors.

DISCUSSION

Unlike cross-sectional studies, the present longitudinal study on HRQoL, anxiety and disease-related coping of school-aged survivors yielded insight into the process of adjustment over time. The first few years of continuous remission after the end of treatment were investigated, in view of the importance of this phase in the run-up to long-term survivorship. The results indicate that, in general, school-aged survivors adjusted well to the cancer experience. Compared with norm data from the general Dutch population, survivors showed worse HRQoL only with respect to Motor Functioning on average 2 months after the end of treatment. From 1 year after treatment, however, survivors did no longer differ from the norm population. We should realize that – on purpose – the data for patients who relapsed were excluded from analysis from the moment of the relapse. Furthermore, survivors having been treated for CNS cancer were not included in the present study.

Our results were in line with the majority of studies among long-term survivors of childhood cancer, in which was found that their overall emotional adjustment as a group was within normal limits (Stam *et al*. 2001). This is not what would be expected considering the stressful experience of childhood cancer and its treatment. It could be partly attributable to the instruments we used. We decided to use generic HRQoL instruments in order to be able to compare the survivors with the general population. The use of cancer-specific instruments, however, is recommended for measuring the impact of childhood cancer longitudinally because this kind of instruments is more sensitive to change. Unfortunately, cancer-specific instruments translated and validated for Dutch school-aged children are not available yet.

Another possible explanation could be 'response shift', which has been described in adults with cancer (Sprangers & Schwartz 1999). The experience with cancer can have changed children's conceptualization of problems, so that fewer problems are being experienced. The good adjustment could also be the result of adequate (family) coping with the stresses of childhood cancer, as is discussed below.

It is important to identify factors that were associated with HRQoL and anxiety so that survivors who are more vulnerable to maladjustment can be traced. None of the medical variables appeared to be associated significantly

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Table 2. Parameter estimates for longitudinal regression models of health-related quality of life (HRQoL) (TNO-AZL Children's Quality of Life questionnaire) in survivors (aged 8–15 years) predicted by measurement occasion, demographic and medical characteristics and disease-related cognitive coping

Fixed effects	Physical Component Scale (TNO-AZL Children's Quality of Life questionnaire)	Mental Component Scale (TNO-AZL Children's Quality of Life questionnaire)
Measurement (deviation from end of treatment; M1)		
1 year (M2)	0.36***	0.36*
2 years (M3)	0.32**	0.54*
3 years (M4)	0.33**	0.61
4 years (M5)	0.44***	0.86
Percentage of explained variance by fixed effects	0.06	0.01
Medical and demographic characteristics†		
Gender (female)	–	–0.32
Age	–	–0.22
Age at diagnosis	–	0.34
Duration of treatment	–0.10	–
Leukaemia or lymphoma (vs. solid tumours)	–	–
Radio- and chemotherapy	–	–
Chemotherapy without radiotherapy	–	–
Prognosis > 75%	0.16	–0.35*
Perceived treatment intensity	–	–
Visible consequences	–	–
Percentage of explained variance by fixed effects	0.10	0.07
Disease-related cognitive coping (Cognitive Control Strategies Scale)		
Predictive control	0.02	0.04
Interpretative control	–0.10*	–0.13*
Vicarious control	0.04	0.13**
Percentage of explained variance by fixed effects	0.13	0.09
Total number of observations	177	177

*$P < 0.1$; **$P < 0.05$; ***$P < 0.01$. The higher the score is the better the HRQoL. Dashes (–) mean that the variables were not included in the model.

†Medical and demographic variables that were not correlated significantly at $P < 0.3$ with Physical Component Scale and/or Mental Component Scale in the initial models were not selected for the final models.

with HRQoL or anxiety. Female survivors, however, reported higher levels of anxiety which is common in the general population. Some correlations were found between disease-related coping and the outcomes. First, survivors who relied more strongly on the expertise of their physician and attributed power to the cancer treatment (*vicarious control*) reported better mental HRQoL (MCS). It is well known that physicians play a role in diminishing disease-related feelings of uncertainty. Second, survivors who were more optimistic about the further course of the disease (*predictive control*) experienced lower levels of anxiety, while those who searched more for information about the disease (*interpretative control*) reported higher levels of anxiety. Causality can not be established but is reasonable to assume that being more optimistic about the further course of the disease can result in lower levels of anxiety. The correlation between interpretative control and anxiety is less clear. On one hand, survivors who feel insecure and anxious may be more in need of information about the disease. On the other hand, the gathered information could reinforce anxiety.

Overall, the variables in the model explained only 13%, 9% and 21% of the variance for PCS, MCS and anxiety respectively. The limited variance explained by the medical variables is not surprising because these variables were assessed rather roughly, and it was too short after termination of treatment for the manifestation of late effects of treatment. Besides, the limited impact of medical variables on HRQoL has been found in many studies among survivors of childhood cancer (Stam *et al*. 2001; Langeveld *et al*. 2002). Undoubtedly, there are other psychosocial variables than the coping variables we assessed in the present study that affect survivors' HRQoL and anxiety, for example, family functioning (Lesko 1990; Rait *et al*. 1992; Kazak *et al*. 1997) and pre-cancer functioning of the survivor.

Limitations and implications

The present study has several limitations that are common in psychosocial research among children. Longitudinal research on children is sparse because different age groups

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Table 3. Parameter estimates for longitudinal regression models of anxiety (State-Trait Inventory for Children) in survivors (aged 8–15 years) predicted by measurement occasion, demographic and medical characteristics and disease-related cognitive coping

Fixed effects	Anxiety (State-Trait Inventory for Children)
Measurement (deviation from end of treatment; M1)	
1 year (M2)	–0.18
2 years (M3)	–0.28
3 years (M4)	–0.16
4 years (M5)	–0.21
Percentage of explained variance by fixed effects	0.004
Medical and demographic characteristics†	
Gender (female)	0.60***
Age	0.11
Age at diagnosis	–0.23
Duration of treatment	–
Leukaemia or lymphoma (vs. solid tumours)	–
Radio- and chemotherapy	–
Chemotherapy without radiotherapy	0.51*
Prognosis > 75%	–
Perceived treatment intensity	–
Visible consequences	–0.13
Percentage of explained variance by fixed effects	0.12
Disease-related cognitive coping (Cognitive Control Strategies Scale)	
Predictive control	–0.18**
Interpretative control	0.18**
Vicarious control	0.00
Percentage of explained variance by fixed effects	0.21
Total number of observations	190

*$P < 0.1$; **$P < 0.05$; ***$P < 0.01$. The higher the score is the higher the level of anxiety. Dashes (–) mean that the variables were not included in the model.
†Medical and demographic variables that were not correlated significantly at $P < 0.3$ with anxiety in the initial models were not selected for the final model.

need different age-specific questionnaires resulting in small sample size. Low power because of small sample size could have contributed to the fact that few variables were found to be predictive of HRQoL and anxiety. Furthermore, because pre-selection of variables for the final analyses was necessary, several medical variables were excluded in the final models which could have led to underestimation of the explained variance of the models. Another disadvantage of the small sample size was that comparison of survivors' anxiety with that of the norm was not possible. In addition, survivors of CNS cancer were not included because these children are underrepresented in the longitudinal VOLG study for logistical reasons.

Despite the small sample size at the last measurement occasion, longitudinal analyses were possible because linear mixed models analyses incorporate all available data into analysis, including data from survivors that missed one or more measurement occasion. Although only 27 observations were available at M5, these observations could still be used to increase the precision of the parameter estimates that are not specific to M5, such as the fixed effects of coping. The attrition of survivors who reached the age of 16 (because of the limited age range of the TACQOL) did probably not bias the results seriously. First, participants did not differ from the non-participants at the several measurement occasions with respect to their outcome scores at T1. Second, the impact of age and medical variables on HRQoL and anxiety was limited in the present study.

Another limitation concerns the outcomes of the study: HRQoL and anxiety. Of course there are other interesting aspects of survivors' functioning, for instance posttraumatic stress, social functioning and educational achievement. It would be of utmost importance to investigate indicators of social functioning because previous studies revealed that school-aged survivors suffered from clinically significant social anxiety, had less friends and participated less in peer and school activities than controls (Spirito *et al.* 1990; Pendley *et al.* 1997; Bessell 2001; Stam *et al.* 2005). On the contrary, Reiter-Purtill *et al.* (2003) concluded that 2 years after diagnosis survivors did not exhibit more social difficulties than peers.

In conclusion, as a group survivors regained good HRQoL after the end of successful cancer treatment in the run-up to survivorship, no doubt, this is an important finding that speaks well for the resilience of the survivors and their parents. However, there is no reason to lean back because of the known (long-term) late effects of many treatments (Oeffinger *et al.* 2006; Geenen *et al.* 2007), whose relationship with survivors' well-being is not clear yet. Although there is little evidence of serious maladjustment, research on more specific paediatric psycho-oncology outcomes demonstrated that there is consistently a group of children and family members (estimated 25–30%) who do not cope well with the cancer or who have personal, family and social difficulties (Patenaude & Kupst 2005). The development of sensitive cancer-related instruments is of utmost importance to be used in psychosocial screening, as few clear medical risk factors for worse psychosocial functioning could be traced until now (Patenaude & Kupst 2005). It is satisfying that monitoring and screening survivors have become standard aftercare in many hospitals in the last decade. Apart from physical and psychosocial screening, the

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standard aftercare should preferably include education and counselling directed at both survivors and their parents. Providing psychosocial information on the effects of the disease and treatment and assisting parents in treating the survivors as normally as possible could prevent late psychosocial problems by enhancing re-entry into normal life.

Giving attention to the cognitive coping strategies of the survivors might be useful when a survivor experiences psychosocial problems. Although the longitudinal analyses in the present study yielded stronger evidence of the presence of causal correlations than do traditional analytic procedures, they can not offer definitive proof of causality between coping and outcomes. This requires an intervention study intended to influence coping. There is evidence of effectiveness for psycho-educational interventions for children with a chronic disease incorporating cognitive-behavioural techniques (Vannatta *et al*. 1998; Plante *et al*. 2001; Barlow & Ellard 2004; Last *et al*. 2007). Further steps in the direction of evidence-based interventions for survivors will be important in the years to come.

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