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Health-related quality of life in adults treated for paediatric acute lymphoblastic leukaemia and their siblings – a longitudinal cohort study.

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Keywords: Health-related quality of life, HRQOL, paediatric, acute lymphoblastic leukaemia, cohort.

Abstract

Introduction Acute lymphoblastic leukaemia (ALL) is the most common form of cancer in children. Although treatment methods have improved and resulted in significant improvement of survival and reduction in late effects and late mortality risk the health-related quality of life (HRQOL) of survivors might be affected. To introduce new interventions in clinical practice with the potential to support positive HRQOL outcomes' more knowledge is needed on how HRQOL in this group is constructed and stimulated. The purpose of this study is to investigate HRQOL in adults treated for paediatric ALL and their siblings in a long-term perspective and factors influencing this relationship.

Methods and analysis This cohort of young adult ALL survivors allow for investigations of factors influencing HRQOL outcomes on a national level. Eligible participants are obtained from the Swedish Childhood Cancer quality registry. Data collection includes both a follow-up of data collected in 2012 (n=224) and recruitment of new eligible participants to the cohort (n=601). The cohort will cover survivors of paediatric ALL, diagnosed between 1985 and 2007, at an age between 0-15 years. Data will be collected using validated, multidimensional, self-administered instruments, designed to measure HRQOL (SF-36), social support (SS-13), sense of coherence (SOC) and resilience (RS). The survey will be administered both digitally and in paper format over a 2-month period.

Ethics and dissemination The study will be carried out in accordance with the ethics permit obtained from the Swedish ethics review authority (Dnr 2019-05181). Dissemination of study results will take place through research articles and reports to the national patient organisation and the national network for consultancy nurses for this target group and to the working group for the Swedish national long-term care program for childhood cancer. Results will also reach practical application within the follow-up clinic for adults after childhood cancer at Sahlgrenska Hospital in Gothenburg.

Article summary

Strengths and limitations of this study

- This study will result in the first cohort for long-term follow-up of HRQOL among young adult ALL survivors in Sweden.
- HRQOL outcomes will be investigated in relation to social support, sense of coherence and resilience, as potential mechanisms of processing the consequences from previous ALL treatment.
- The importance of antecedents and health status for the relationships between HRQOL and social support, sense of coherence and resilience will be investigated.
- How HRQOL changes over time by comparing longitudinal data collected in 2012 and 2021.
- Findings based on quantitative data will be supplemented with findings from qualitative data on the experiences of factors that have affected HRQOL.

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common form of cancer in children with the main incidence occurring between ages 2 to 4 years. However, the disease also occurs in adulthood with about 30 to 40 cases per year between the ages of 15 and 45, and since 2008 these groups are treated with the same treatment protocol. Prognosis has improved significantly and continuously since the 1960s, which with current treatment and knowledge has increased the 5-year survival rate to over 90% for children and to about 75% for adults [1-3]. Over time, treatment methods have improved, and the late mortality risk has decreased [4]. However, the frequency of late complications is still high, even if the pattern of complications has changed. Large longitudinal studies from the United States have shown that life threatening complications in survivors treated during 1991-2007 has decreased compared with earlier treatment protocols, mainly due to the reduction of cranial irradiation [5]. Fortunately, the vast majority survivors from standard-risk ALL, not treated with cranial irradiation, have been shown to have a life that is physically, psychosocially and socioeconomically similar to that of the general population [6].

However, it has been shown that children, who have been treated for ALL and have been in remission for 2 to 13 years, have a more negative self-image and experience a lower health-related quality of life (HRQOL) than their siblings [7]. A literature review [8] shows a large variation in results in research reporting both higher, lower, and comparable HRQOL in young and adult survivors of paediatric ALL compared to control groups. Only a few studies have examined the relationship between psychosocial factors, such as coping and resilience, and HRQOL, but the results available indicate that such factors can have protective effects. However, there are no prospective studies investigating such relationships and that can provide a more in depth understanding of the determinants of HRQOL and other health outcomes for this group [8].

A common instrument for self-assessment of HRQOL is SF-36, whose validity and reliability has been specifically examined among adult survivors of paediatric cancer [9]. The instrument is constructed around various different parameters that reflect different health conditions. One reason for the wide variety of results from studies examining HRQOL may be the complexity of the measure. When a person is diagnosed with a life-threatening illness such as ALL, an adaptation process begins that alters the person's perception of their HRQOL. This process can explain how the HRQOL experience changes over time in connection with illness and how it is affected by antecedents (e.g. gender, education, personality, self-esteem) and various influencing factors (e.g. resilience, social support) [10]. The adaptation process involves a change in the understanding of what HRQOL is, a so-called, response-shift, which in turn has an effect the individual's perception of their own HRQOL. This means that the behavioural, cognitive and affective processes that occur in connection with changes in an individual's health status can have an indirect effect on that persons own HRQOL [10]. This iterative and dynamic process begins with the onset of the disease and continues both during and long after treatment has ended and is therefore important to understand in order to target which supportive resources that should be provided and tailored to individual needs and conditions to promote as favourable HRQOL outcomes as possible. To achieve this, longitudinal studies of changes in HRQOL and the importance of antecedents and influence factors are required.

The prevalence of mental illness among adults who survived cancer as a child has only been investigated to a limited extent. The studies available shows an increased prevalence, which indicates the need for more research in the field [11]. The importance of fatigue and lower vitality may in itself be a relevant factor to study more closely among those who survived paediatric ALL. Fatigue is common in both mental illness as well as complex pain disorders (e.g. chronic widespread pain) and lower vitality (estimated by SF-36) have been shown to predict the onset of chronic widespread pain even in previously pain-free individuals [12]. Qualitative studies based on interviews with adults who have survived ALL can increase understanding of the adaptation process in relation to the experience of HRQOL and how it changes over time and how it can be supported in different ways. It has been found that some adults who survived paediatric ALL describe that as children they wanted to be more involved in their care and also receive more continuous support to be able to manage and process the physical, mental and social consequences of the disease, and in order to continue live after the disease [13]. In order to increase the possibility of introducing new supportive interventions in clinical practice, more knowledge is needed on how the HRQOL among adults who have survived cancer is constructed and stimulated. It is also important to further understand how their siblings experience their HRQOL and the potential effects of growing up with a sibling with ALL.

The purpose of this study is to investigate HRQOL in adults treated for paediatric ALL and their siblings in a long-term perspective. The study is divided into several specific goals that are structured based on the response shift theory as an explanatory model for how self-assessed HRQOL changes in connection with a traumatic event (Figure 1). The specific goals are:

- To describe the relationship between HRQOL and social support, sense of coherence and resilience, as potential mechanisms of processing the consequences from previous ALL treatment, resulting in adaptation and restoration of HRQOL.
- To describe the importance of antecedents and health status for the relationships between HRQOL and social support, sense of coherence and resilience.
- To describe the relationship between HRQOL and health care consumption and sick leave.
- To describe how HRQOL changes over time by comparing longitudinal data collected in 2012 and 2021.
- To investigate the experiences of factors that have affected HRQOL.

Figure 1. Model for project logic based on the response shift theory [10].

Methods

Design:

The study is a long-term follow-up of a cohort consisting of adult paediatric ALL survivors and their siblings, established in 2012. It also includes explorative interviews with a selection of participants.

Participants:

All participants included in the data collection in 2012 will be invited to participate in the follow-up study. All individuals registered in the Swedish Childhood Cancer quality registry in 2012, diagnosed with ALL between 1985 and 1997 were eligible for inclusion (n=416). In 42 cases, the presence of mental health problems, disabilities (downs syndrome), emigration or longer stays abroad was confided. Out of the remaining 374 individuals 224 (60%) completed the questionnaire after up to two reminders. In this follow-up of the 2012 data collection, additional participants will be recruited from the same registry among those diagnosed between 1998 and 2007 (n=601). In total, the cohort, through the new recruitment, will cover people who survived paediatric ALL, diagnosed between 1985 and 2007, at an age between 0-15 years. The follow-up of data collected in 2012, opens up for investigating how time (chronologically) influences health outcomes in these groups. In 2012, siblings were recruited (n=70) through the included ALL survivors (by the questionnaire) and a similar procedure will be repeated at follow-up.

Data collection:

Data will be collected during the first quarter of 2021 and will be based on the questionnaire used in 2012 which included validated instruments for HRQOL (SF-36) [14] and a number of variables with potential influence on HRQOL, such as socio-demographics (family, education, employment, income), life style (physical activity, sleep, alcohol and tobacco), general self-efficasy (GSES) [15 16], social support (SS-13) [17], resilience (RS) [18 19], sense of coherence (SOC) [20], mental health (DASS 21) [21], physical health (CCI) [22], musculoskeletal pain (prevalence) [23], fatigue (MFI-20) [24], and sick leave and health consumption (self-reported and registry based). The questionnaire will be digital and invitations to participate with the link to the digital questionnaire and informed consent forms will be sent out by ordinary mail. Reminders will be sent out with 2-week intervals and with the second reminder, a paper version of the questionnaire will be sent along and will be followed by final reminder. Data collection will end 2-weeks after the final reminder and thereby close the 2-month data collection period. This process, with a digital questionnaire and several reminders, will increase the probability of getting as high a response rate as possible and reduce missing data both in terms of participants failing to answer all questions in the questionnaire and dropouts of participants. Upon submission of the questionnaire there will also be an invitation to participate in a semi-structured telephone interview (n=25 for both participants treated for paediatric ALL and their siblings). In order to obtain a maximum variety of experiences, the selection of participants for the interviews will be made strategically, based on the responses from the questionnaire. This means that the selection will be made by participants being deliberately selected to achieve variation regarding, for example, gender, age, work experience, and experience of HRQOL.

Analysis:

Data analysis will be carried out during 2021-2022. Quantitative data will be analysed using different statistical methods depending on the research questions to be answered. In a first step, associations between (theoretically identified) dependent and independent variables will analysed by multiple regressions. Further, the structural relationship between observed and latent variables, allowing the variables to act as both dependent and independent variables (see Figure 1), will be analysed by structural equation modelling (SEM). The size of the study population and the expected response rate of between 60-70% allow a sufficient number of

responses to meet the requirements on population size for statistical power given the validity and reliability assessments of the included instruments.

The qualitative interviews will be analysed according to phenomenographic methodology. After transcription, each interview will be listened to and transcripts read several times for familiarization and to get an overall impression of the data material. Each interview will be processed by searching for statements that correspond to the purpose of the study (condensation), which will then be analysed to find similarities and differences (comparison). The condensed statements will then be grouped based on their characteristic features (grouping) and similarities between the groups will be described (articulation) and then referred to as categories (labelling). The final step in the analysis is to compare the different categories in terms of similarities and differences to ensure that the categories has unique characteristics and are on the same level of description (contrasting). Throughout the analysis, there is a constant interaction between the different stages and continuous discussion and confirmation of the process and developed results between the researcher performing the analysis and the rest of the research team. The team include a broad range of competence backgrounds both in qualitative research methodology and the clinical context and research field.

The Patient and Public Involvement:

The cohort was initially established based on interaction with children with ALL and their parents as well as with healthcare practitioners involved in the medical and social care of patients with paediatric ALL and with a local patient organisation for this group of patients. This interaction took place within the boundaries of a research-based design project aiming to develop social support for young survivors of ALL. It demonstrated the need to monitor long-term HRQOL and specific influencing factors within this target group. The establishment of the cohort took place in consultation with clinicians at a regional paediatric cancer centre and the Swedish Childhood Cancer Registry. The is and will continue to be target group influence over the data created in the cohort since; a) the collected variables are based on HRQOL issues established in interaction with the target group and relevant stakeholders and b) as data in the cohort is based on the participants' self-reported experiences.

Ethics and dissemination:

The study will be carried out in accordance with the ethics permit obtained from the Swedish ethics review authority (Dnr 2019-05181), All collected data will be treated confidentially and the participants will not be able to be identified due to coding of all data material. The results in the study will only be presented at group level without the possibility of identifying individuals. Participation in the study is voluntary and based on informed consent. Each participant will be able to withdraw their participation at any time without having to justify why. The project will contribute to development of knowledge that is of benefit to a group with increased risk of HRQOL problems later in life and investigating such risks can contribute to improving care both to children who are currently undergoing treatment for ALL and to children and adults who have undergone treatment earlier in life. Dissemination of study results will take place through reports to the national patient organisation for this target group, the national network for consultancy nurses for this target group and to the working group for the Swedish national long-term care program for childhood cancer. Results will also

reach practical application within the follow-up clinic for adults after childhood cancer at Sahlgrenska Hospital in Gothenburg.

Results

The cohort established in 2012 consists of young adult people diagnosed with paediatric ALL between 1985 and 1997 (n = 224) and their siblings (n = 70). Analysis of baseline data has shown significant differences between those who survived paediatric ALL and their siblings regarding the SF-36 dimensions general health (69.6 ± 3.0 and 78.4 ± 4.3) and emotional functioning (77.1 ± 4.6 and 88.1, respectively). ± 1.2) [25]. In comparison to norm values, both survivors of paediatric ALL and their siblings estimated a lower vitality (56.9 ± 2.9 and 57.4 ± 4.8) than the norm (68.8 ± 1.1), and a lower mental health (71.3 ± 2.6 and 76.1 ± 3.7, respectively) than the norm (80.9 ± 0.9). Regarding sleep, the proportion who slept less than five hours, and the proportion who slept more than 9 hours were higher among the ALL survivors, although the differences were not significant (p = 0.066). Previous research has shown that the number of hours of sleep has a U-shaped relationship with health, indicating an optimum of 7 hours of sleep, and an increasing risk for mortality when >8 hours of sleep and <6 hours of sleep [26].

In the data collected 2012, we could also see that a larger proportion of the siblings were students, while a larger proportion of the ALL survivors were at work, unemployed or on sick leave, which indicates a difference in the groups' introduction to the labour market which is worth following up to assess the potential variance in socioeconomic factors between the groups in adulthood.

There was no age difference between those who survived paediatric ALL and their siblings (28.5 ± 4.0 and 29.1 ± 6.4, respectively). At the planned follow-up in 2020, participants will be around 37 years old, and will have reached an age where they are expected to take responsibility for work and their own family. Therefore, in order to get an idea of the long-term effects of paediatric ALL, it is important to follow the group during this time when they are increasingly exposed to external risk factors, and when they have reached an age which in itself entails an increased risk of ill health.

The study is a collaboration between researchers at Halmstad University and the paediatric cancer long-term follow-up unit at the Sahlgrenska University Hospital in Gothenburg. The previous research from the research group has studied the long-term effects of cancer illness and treatment on young people's health outcomes and how follow up care, social support and increased participation during care can be provided to the target group. The research has resulted in both development of care processes and organisation and digital support service that have been tested and implemented in clinical practice. Members of the research group are part of national and Nordic clinical networks for late effects among paediatric cancer survivors and participate in the development and follow up of the Swedish national long-term follow-up care program for childhood cancer.

Conclusions

As treatment outcomes for ALL have improved, the importance of long-term follow-up and handling of late effects has increased, both during childhood and in adulthood. This is the main purpose of the Swedish national Guidelines for long-term follow-up after paediatric cancer treatment. A prerequisite for the work on the national guidelines is research that follows this target group long-term and maps trends and relationships around risk factors and protective factors. Such knowledge from research can supplement the clinical experience and provide guidance for continuous improvement work on long-term follow-up after childhood cancer. The current cohort is based on national recruitment of participants and has a relatively good response rate. Studies based on the cohort can therefore be considered generalizable in a national context.

Author contributions

JN, KA and SA drafted the outline of the study and all authors participated in writing the protocol.

Funding statement

The 2012 data collection was funded by a Swedish Research council grant (Award/Grant number is not applicable) to JN and the follow-up data collection has received funding from Halmstad University (Award/Grant number is not applicable) to JN, KA and SA.

Data availability statement

The ethical approval for this study does not allow for the sharing of raw data collected in the cohort based on the risk of revealing the participants' identities at subgroup level.

Competing interests' statement

The authors have no competing interests to declare.

Word count

2,787 words.

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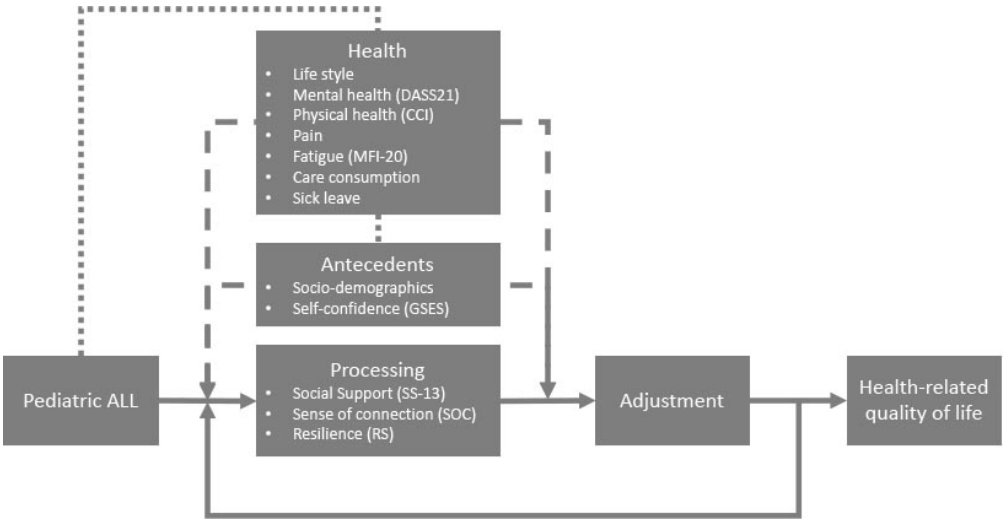

Figure 1. Model for project logic based on the response shift theory.

287x147mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies (von Elm et al 2007)*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	5-6

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	-
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	-
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative.
The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies.
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Health-related quality of life in adults treated for paediatric acute lymphoblastic leukaemia – a cross-sectional and longitudinal cohort study.

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Health-related quality of life in adults treated for paediatric acute lymphoblastic leukaemia – a cross-sectional and longitudinal cohort study.

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Keywords: Health-related quality of life, HRQOL, paediatric, acute lymphoblastic leukaemia, cohort.

Abstract

Introduction Acute lymphoblastic leukaemia (ALL) is the most common form of cancer in children. Although treatment methods have improved and resulted in significant improvement of survival and reduction in late effects and late mortality risk, the health-related quality of life (HRQOL) of survivors might be affected. To introduce new interventions in clinical practice with the potential to support positive HRQOL outcomes' more knowledge is needed on how HRQOL in this group is constructed and stimulated. The purpose of this study is to investigate how HRQOL is affected in adults treated for paediatric ALL, in a long-term perspective and possible factors influencing this relationship.

Methods and analysis This cohort of young adult ALL survivors allow for investigations of factors influencing HRQOL outcomes on a national level. Eligible participants are obtained from the Swedish Childhood Cancer quality registry. Data collection includes both a follow-up of data collected in 2012 (n=224) and recruitment of new eligible participants to the cohort (n=601). The cohort will cover survivors of paediatric ALL, diagnosed between 1985 and 2007, at an age between 0-15 years. Data will be collected using validated, multidimensional, self-administered instruments, designed to measure HRQOL (SF-36), social support (SS-13), sense of coherence (SOC) and resilience (RS).

Ethics and dissemination The study will be carried out in accordance with the ethics permit obtained from the Swedish ethics review authority (Dnr 2019-05181). Dissemination of study results will take place through research articles and reports to the national patient organisation and the national network for consultancy nurses for this target group and to the working group for the Swedish national long-term care program for childhood cancer. Results will also reach practical application within the follow-up clinic for adult childhood cancer survivors at Sahlgrenska Hospital in Gothenburg.

Article summary

Strengths and limitations of this study

- The patient cohorts are recruited on population-based data from the National Childhood Cancer Registry
- The follow-up of data collected in 2012, opens up for investigating how time (chronologically) influences health outcomes in these groups. HRQOL changes over time by comparing longitudinal data in cohort 1 and 2 collected in 2012 and 2021.
- The outcomes will also be investigated in relation to data from other health care registries including number of days on sick leave and other welfare subsidise. …..
- The importance of antecedents and health status for the relationships between HRQOL and social support, sense of coherence and resilience will be investigated.
- Findings based on quantitative data will be further explored with interviews to collect and analyse qualitative data on the experiences of factors that have affected HRQOL.
- HRQOL outcomes will be investigated in relation to social support, sense of coherence and resilience, as potential mechanisms of processing the consequences from previous ALL treatment.

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common form of cancer in children with the main incidence occurring between ages 2 to 4 years. In Sweden, there are approximately 100 new cases each year with ALL up to the age of 18 years. The prognosis has improved significantly and continuously since the 1960s, from almost non-existing to a 5-year survival rate to over 90% in the latest Nordic ALL protocol[1-3]. Over time, treatment methods have improved, and the late mortality risk has decreased [4]. However, the frequency of late complications is still high, even if the pattern of complications has changed. Large longitudinal studies from the United States have shown that life threatening complications in survivors treated during 1991-2007 has decreased compared with earlier treatment protocols, mainly due to the reduction of cranial irradiation [5]. Fortunately, the vast majority survivors from standard-risk ALL not treated with cranial irradiation, have been shown to have a life that is physically, psychosocially and socioeconomically similar to that of the general population [6].

However, children treated for ALL and have been in remission for 2 to 13 years, have been shown a more negative self-image and experience a lower health-related quality of life (HRQOL) than their siblings [7]. A literature review [8] shows a large variation in results in research reporting both higher, lower, and comparable HRQOL in young and adult survivors of paediatric ALL compared to control groups. Only a few studies have examined the relationship between psychosocial factors, such as coping and resilience, and HRQOL, but the results available indicate that such factors may have protective effects. However, there are no longitudinal studies investigating such relationships possibly providing depth understanding of the determinants of HRQOL and other health outcomes for this group [8].

A common instrument for self-assessment of HRQOL is SF-36, whose validity and reliability has been specifically examined among adult survivors of paediatric cancer [9]. The instrument covers eight different dimensions of HRQOL: physical functioning, social functioning, role limitations due to physical functioning (role functioning—physical), bodily pain, general mental health, role limitations due to emotional functioning (role functioning—emotional), vitality (energy and fatigue), and general health perception. One reason for the wide variety of results from studies examining HRQOL may be the complexity of the measure. When a person is diagnosed with a life-threatening illness such as ALL, an adaptation process begins that alters the person's perception of their HRQOL. This process can explain how the HRQOL experience changes over time in connection with illness and how it is affected by antecedents (e.g. gender, education, personality, self-esteem) and various influencing factors (e.g. resilience, social support) [10]. The adaptation process involves a change in the understanding of what HRQOL is, a so-called, response-shift, which in turn has an effect the individual's perception of their own HRQOL. This means that the behavioural, cognitive and affective processes that occur in connection with changes in an individual's health status can have an indirect effect on that persons own HRQOL [10]. This iterative and dynamic process begins with the onset of the disease and continues both during and long after treatment has ended. Since most patients with ALL are treated in early childhood this process is even more complex involving parents and sibling. The process is important to understand in order to target adequate supportive resources tailored to individual needs and conditions to promote as favourable HRQOL outcomes as possible. To achieve this, longitudinal studies of changes in HRQOL and the importance of antecedents and influence factors are required.

The prevalence of mental illness among adults who survived cancer as a child has only been investigated to a limited extent. The studies available shows an increased prevalence, which indicates the need for more research in the field [11]. The importance of fatigue and lower vitality may in itself be a relevant factor to study more closely among those who survived paediatric ALL. Fatigue is common in both mental illness as well as complex pain disorders (e.g. chronic widespread pain) and lower vitality (estimated by SF-36) have been shown to predict the onset of chronic widespread pain even in previously pain-free individuals [12]. Qualitative studies based on interviews with adults who have survived ALL can supplement quantitative data from questionnaires and give an experience-based understanding of the adaptation process in relation to the HRQOL; how it changes over time and how it can be supported in different ways. It has been found that some adults who survived paediatric ALL describe that they as children wanted to be more involved in their care and also receive more continuous support to be able to manage and process the physical, mental and social consequences of the disease, to continue life after the disease [13]. To increase the possibility of introducing new supportive interventions in clinical practice, more knowledge is needed on how the HRQOL among adults who have survived cancer is affected and positively stimulated.

Objectives:

The main purpose of this study is 1) to describe the development of HRQOL over time, and 2) to investigate factors of importance for HRQOL in adults treated for paediatric ALL.

This will be studied by investigating HRQOL in adult survivors of paediatric ALL based on the hypothesis that HRQOL in adult paediatric ALL survivors is associated with a) time for treatment and age at follow-up, and b) background factors.

a) *The significance of age and time* will be investigated by describing the changes of HRQOL over time from young adulthood to 10-years later, and by investigating differences in HRQOL between young adults treated for paediatric ALL in 1985-1997 and young adults treated in 1997-2007.

b) *Factors of importance for HRQOL* in adult survivors of paediatric ALL will be studied by investigating associations between HRQOL and several potentially buffering background factors such as sociodemographic factors, lifestyle, social support, sense of coherence and resilience, as well as associations with care consumption and sickness absence. For a holistic perspective, factors of importance for HRQOL will also be investigated by qualitative studies describing experiences from adult survivors of paediatric ALL.

Methods

Design:

The study is a cross-sectional and longitudinal cohort study based on questionnaire data that will be collected in 2021 as part of a long-term follow-up of a cohort consisting of adult survivors of paediatric ALL, established in 2012. Analysis of baseline data from the cohort established in 2012 has shown significant differences in comparison to norm values. Survivors of paediatric ALL estimated a lower vitality (56.9 ± 2.9) than the norm (68.8 ± 1.1), and a lower mental health (71.3 ± 2.6) than the norm (80.9 ± 0.9) [14]. At the planned follow-

up in 2021, participants will be around 37 years old, and will have reached an age where they are expected to take responsibility for work and their own family. Therefore, in order to get an idea of the long-term effects of paediatric ALL, it is important to follow the group during this time when they are increasingly exposed to external risk factors, and when they have reached an age which in itself entails an increased risk of ill health. The data collection in 2021 will also include a cross-sectional study of adult survivors of paediatric ALL treated 1985-2007 and explorative interviews with a selection of participants.

Participants:

All participants included in the data collection in 2012 will be invited to participate in the follow-up study. All individuals registered in the Swedish Childhood Cancer quality registry in 2012, diagnosed with ALL between 1985 and 1997 were eligible for inclusion (n=416). In 42 cases, the presence of mental health disorders or disabilities (downs syndrome), emigration or longer stays abroad was confided by relatives and prevented their participation. Out of the remaining 374 individuals 224 (60%) completed the questionnaire after up to two reminders. In this follow-up of the 2012 data collection, additional participants will be recruited from the same registry among those diagnosed between 1998 and 2007 (n=601). In total, the cohort, through the new recruitment, will cover people who survived paediatric ALL, diagnosed between 1985 and 2007, at an age between 0-15 years. The follow-up of data collected in 2012, opens up for investigating how time (chronologically) influences health outcomes in these groups.

Data collection:

Data will be collected with a questionnaire and interviews from March – December 2021. The questionnaire will be based on the variables used in 2012 which included validated instruments for HRQOL (SF-36) [15] and a number of variables with potential influence on HRQOL, such as socio-demographics (family, education, employment, income), life style (physical activity, sleep, alcohol and tobacco), general self-efficasy (GSES) [16, 17], social support (SS-13) [18], resilience (RS) [19, 20], sense of coherence (SOC) [21], mental health (DASS 21) [22], physical health (CCI) [23], musculoskeletal pain (prevalence) [24], fatigue (MFI-20) [25], and sick leave and health consumption (based on self-report and national registry data). The questionnaire will be digital and invitations to participate with the link to the digital questionnaire and informed consent forms will be sent out by ordinary mail. Reminders will be sent out with 2-week intervals and with the second reminder, a paper version of the questionnaire will be sent along and will be followed by final reminder. Data collection will end 2-weeks after the final reminder and thereby close the 2-month data collection period. This process, combining a digital questionnaire, several reminders and a final reminder with a paper version of the questionnaire, will increase the probability of getting as high a response rate as possible by inviting to participate both digitally and on paper and also reduce missing data both in terms of participants failing to answer all questions in the questionnaire and dropouts of participants. To supplement the self-report data several objective clinical parameters for the participants will be collected from the Swedish Childhood Cancer quality registry, such as the treatment protocol used, risk classification, chemotherapy, radiation, bone-marrow transplantation, relapse, secondary malignancy. Upon submission of the questionnaire there will also be an invitation to participate in a semi-structured telephone interview (n=40) performed by a researcher who is experienced in

qualitative methodology and interviews with informants in sensitive contexts (SA). In order to obtain a maximum variety of experiences, the selection of participants for the interviews will be made strategically, based on the responses from the questionnaire. This means that the selection will be made by participants being deliberately selected to achieve variation regarding, for example, intensity of treatment, gender, age, work experience, and experience of HRQOL. The interviews have an exploratory approach with open-ended questions. The interview guide begins with a question about the informant's experiences of being treated for leukemia as a child. This is followed by questions related to health, quality of life and lifestyle, where the informants are allowed to describe what it means to them, how it is for them today and how it has been affected by having been treated for leukemia as a child. Finally, the recommendations that the informant would like to give to health care professionals who currently care for children with leukemia are touched upon. In order to gain an increased understanding of what the informants express, follow-up questions will be asked, such as: Can you describe it in a little more detail? How do you mean?

Analysis:

Data analysis will be carried out during the end of 2021 to end of 2022. Quantitative data will be analysed using different statistical methods depending on the research questions to be answered. In a first step, HRQOL will be described by presenting mean values and standard deviations. The aspect of changes in HRQOL during adulthood will be investigated by using data from the cohort providing data in 2012 and 2021. For analyses when investigating the association between time for treatment and HRQOL, a comparison and test for difference in mean HRQOL between the two groups (one entering the study in 2012, the other group entering the study in 2021) will be made. When investigating factors of importance for HRQOL univariate and multiple regression analyses will be used. The size of the study population and an assumed response rate of 60-70% should allow for a sample size sufficient for evaluations of small differences in HRQOL outcomes between groups, using the SF-36 instrument [26].

The qualitative interviews will be analysed according to phenomenographic methodology as it allows to focus on how the informants perceive a certain phenomenon or aspect of the world. In the analysis, attention is directed to “how” the phenomenon is perceived and describing the variation in perceptions [27]. The analysis will be performed by two experienced researchers in qualitative methodology (SA and MO). After transcription, each interview will be listened to and transcripts read several times for familiarization and to get an overall impression of the data material. Each interview will be processed by searching for statements that correspond to the purpose of the study (condensation), which will then be analysed to find similarities and differences (comparison). The condensed statements will then be grouped based on their characteristic features (grouping) and similarities between the groups will be described (articulation) and then referred to as categories (labelling). The final step in the analysis is to compare the different categories in terms of similarities and differences to ensure that the categories has unique characteristics and are on the same level of description (contrasting). Throughout the analysis, there is a constant interaction between the different stages and continuous discussion and confirmation of the process and developed results between the researchers performing the analysis and the rest of the research team. The team include a broad range of competence backgrounds both in qualitative research methodology and the clinical context and research field.

The Patient and Public Involvement:

The cohort was initially established based on interaction with children with ALL and their parents as well as with healthcare practitioners involved in the medical and social care of patients with paediatric ALL and with a local patient organisation for this group of patients. This interaction took place within the boundaries of a research-based design project aiming to develop social support for young survivors of ALL. It demonstrated the need to monitor long-term HRQOL and specific influencing factors within this target group. The establishment of the cohort took place in consultation with clinicians at a regional paediatric cancer centre and the Swedish Childhood Cancer Registry. The is and will continue to be target group influence over the data created in the cohort since; a) the collected variables are based on HRQOL issues established in interaction with the target group and relevant stakeholders and b) as data in the cohort is based on the participants' self-reported experiences.

Ethics and dissemination:

The study will be carried out in accordance with the ethics permit obtained from the Swedish ethics review authority (Dnr 2019-05181), All collected data will be treated confidentially and the participants will not be able to be identified due to coding of all data material. The results in the study will only be presented at group level without the possibility of identifying individuals. Participation in the study is voluntary and based on informed consent. Each participant will be able to withdraw their participation at any time without having to justify why. The project will contribute to development of knowledge that is of benefit to a group with increased risk of HRQOL problems later in life and investigating such risks can contribute to improving care both to children who are currently undergoing treatment for ALL and to children and adults who have undergone treatment earlier in life. Dissemination of study results will take place through reports to the national patient organisation for this target group, the national network for consultancy nurses for this target group and to the working group for the Swedish national long-term care program for childhood cancer. Results will also reach practical application within the follow-up clinic for adults after childhood cancer at Sahlgrenska Hospital in Gothenburg.

Strengths and limitations

A few strengths and limitations should be mentioned in relation to this study. A strength of the study is that it focuses on a well-defined patient group that corresponds to about a third of all childhood cancer cases annually in Sweden. The advantage of this is that variations that are specific to different types of cancer diagnoses and their treatment protocols do not occur in the study and therefore do not have an impact on the study results. The disadvantage is that the number of eligible informants is reduced. In the data collection in 2012 a portion of the eligible participants did not complete the survey. We do not have ample data on these non-responders allowing for interpretations on how representative the participants were in relation to the total number of eligible participants; however, we could see that the non-responders were evenly distributed between men and women, were of similar age as the participants and had similar geographical distribution nationally as the participants.

It should be highlighted that although the response shift process is underlined in this study, as important to understand how HRQOL develops over time following treatment for pediatric

ALL, the actual response shift effect itself will not be investigated as part of the study. Rather, the focus is on the importance of several factors that might influence HRQOL outcomes on individual level. These will be investigated to increase knowledge on what factors that might be relevant for response shift processes for this particular group and that should be further researched.

A strength of the study is that it is based on a collaboration between academic researchers at Halmstad University and clinically active researchers at the paediatric cancer long-term follow-up unit at the Sahlgrenska University Hospital in Gothenburg. Previous research from the research group has studied the long-term effects of cancer illness and treatment on young people's health outcomes and how follow up care, social support and increased participation during care can be provided to the target group. The research has resulted in both development of care processes and practice and the design of digital support services tested in clinical practice. Members of the research group are part of national and Nordic clinical networks for late effects among paediatric cancer survivors and participate in the development and follow up of the Swedish national long-term follow-up care program for childhood cancer allowing for feasible dissemination.

As treatment outcomes for ALL have improved, the importance of long-term follow-up and handling of late effects has increased, both during childhood and in adulthood. This is the main purpose of the Swedish national Guidelines for long-term follow-up after paediatric cancer treatment. A prerequisite for the work on the national guidelines is research that follows this target group long-term and maps trends and relationships around risk factors and protective factors. The current cohort is based on national recruitment of participants and has a relatively good response rate. Studies based on the cohort and long-term follow up of outcomes can therefore be considered generalizable in a national context. Such studies can also supplement the clinical experience and provide guidance for continuous improvement work on long-term follow-up after childhood cancer.

Author contributions

All authors, KA, SA, MO, MJ, JMN, participated in the conception and design of the study, planned the data collection and analysis, and participated in writing the article.

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Competing interests' statement

The authors have no competing interests to declare.

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3,165 words.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies (von Elm et al 2007)*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	5-6

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	-
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	-
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative.
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