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RESEARCH ARTICLE

Clinical evaluation of late outcomes in Dutch childhood cancer survivors: Methodology of the DCCSS LATER 2 study

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Abstract

Background: Childhood cancer survivors face late health problems; despite advances in research, details on risk remain unclear. We describe the methodological aspects of the Dutch Childhood Cancer Survivor Study (DCCSS) cross-sectional clinical study (LATER 2 study).

Procedure: From the multi-center DCCSS LATER cohort of 6165 five-year survivors diagnosed during 1963–2001, we invited 4735 eligible survivors in 2016, as well as siblings and parents of survivors. Gaps in evidence identified during development of surveillance guidelines were translated into clinical research questions for 16 outcome-specific subprojects. The regular care visit to the LATER outpatient clinic

Abbreviations: DCCSS, Dutch Childhood Cancer Survivor Study; DNA, deoxyribonucleic acid; DXA, dual-energy x-ray absorptiometry.

forms the backbone of outcome assessment complemented with research-defined measurements (physical examination, clinical tests, questionnaires). Furthermore, blood/saliva samples were taken for deoxyribonucleic acid (DNA) extraction.

Results: In total, 2519 (53.2%) survivors participated in the LATER 2 study. When comparing participants with nonparticipants, we observed that males, CNS survivors, and those treated with surgery only were less likely to participate. Of the participating survivors, 49.3% were female. Median time since childhood cancer diagnosis was 26.9 years (range 14.8–54.7 years) and median attained age was 34.4 years (range 15.4–66.6 years).

Conclusions: The high-quality data generated in the LATER 2 study will provide valuable insights into risks of and risk factors for clinical and physical and psychosocial health outcomes and factors for early recognition of those health outcomes in long-term childhood cancer survivors. This will contribute to fill in important gaps in knowledge and improve the quality of life and care for childhood cancer survivors.

KEYWORDS
childhood cancer survivors, clinical study, late outcomes, methodology, questionnaires

1 | INTRODUCTION

Advances in diagnosis and treatment of childhood cancer over the last decades have dramatically increased long-term survival, with a 5-year overall survival of more than 80%.[1] As a result, the number of childhood cancer survivors is growing, and it has become increasingly clear that the former disease and its treatment can significantly impair long-term physical and psychosocial health leading also to premature mortality.[2–5]

In 2010, the Dutch Childhood Cancer Survivor Study (DCCSS) LATER collaborative group finalized the LATER guideline for surveillance of late effects in survivors of childhood cancer and identified clinically relevant gaps in knowledge.[6] The DCCSS group of clinicians, researchers, and representatives from the patient–parent organization made a research agenda for survivorship research in the Netherlands based on the gaps of knowledge in guidelines and their own expertise, which forms the basis of the DCCSS LATER study. Decisions on which topics will be addressed in the DCCSS LATER study are made in consensus. The DCCSS LATER study currently consists of two parts (Figure 1). In the LATER 1 observational study, outcomes on health conditions were collected through questionnaires and linkages to national registries. The methods for this study are described in a separate paper.[7]

In this paper, we describe the methodology and provide the first baseline characteristics of participants of the LATER 2 study, which involves clinical measurements. All cohort members alive in 2016 were invited to participate in this cross-sectional study. The goals of the LATER 2 study are (a) to identify and characterize populations at high risk for medical and/or psychosocial chronic health conditions associated with childhood cancer, its treatment, and other risk factors such as lifestyle; (b) to identify accurate screening tests for adverse health outcomes in survivors of childhood cancer; (c) to get insight into the pathophysiological mechanisms and genetic predispositions underlying the multi-factorial etiology of the studied health outcomes; and (d) to identify subgroups of survivors who may benefit from interventions and preventive measures and to identify subgroups who will likely not benefit from such actions.

To achieve these goals, the DCCSS LATER study group designed, a priori, 16 sub-studies based on health outcomes (Table S1). Eligible survivors were invited to undergo clinical tests and questionnaires for

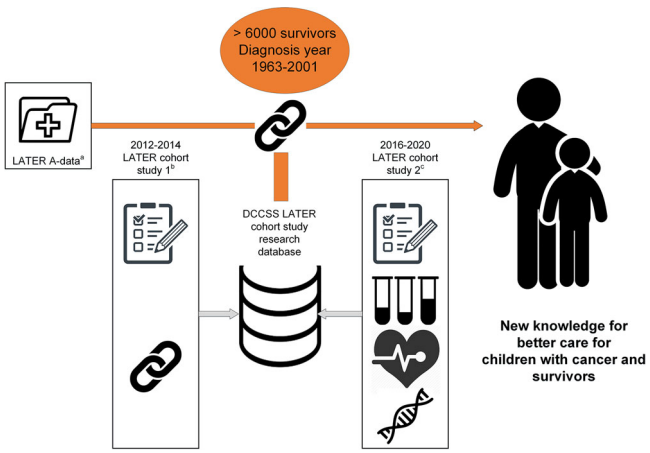

FIGURE 1 Overview of the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort and specific study parts. (A) LATER A-data includes data on patient characteristics, childhood cancer characteristics, and treatment characteristics. (B) Icons depict examples of outcomes that were collected during the LATER 1 study. For a complete overview of the LATER 1 study, see Teepen et al. "Questionnaire- and linkage-based outcomes in Dutch childhood cancer survivors: methodology of the DCCSS LATER study part 1."[7] (C) Icons depict examples of outcomes that were collected during the LATER 2 study.

research purposes, in addition to the clinical tests during regular care, based on the LATER guidelines. This paper describes the methodological aspects of the LATER 2 study; clinical visit, and questionnaire study. The specific methodologies of sub-studies will be described in separate papers.

2 | METHODS

The DCCSS LATER 2 study is a cross-sectional study within the multicenter LATER cohort of 6165 five-year survivors of childhood cancer, who were initially diagnosed between 1963 and 2001 in the seven pediatric oncology centers in the Netherlands (Amsterdam University Medical Center [VU Medical Center and Academic Medical Center], Leiden University Medical Center, Erasmus Medical Center Rotterdam, University Medical Center Groningen, Radboudumc Nijmegen, and University Medical Center Utrecht).[7] Since 2018, pediatric oncology care is centralized in the new Princess Máxima Center. Long-term follow-up care takes place in the Princess Máxima Center for survivors who transitioned from their original treatment center to the Princess Máxima Center or in the original treatment center for those who did not transition.

2.1 | Participants LATER 2 study

2.1.1 | Childhood cancer survivors

Survivors included in the LATER cohort were traced via the Municipal Personal Records Database (Dutch: Basisregistratie Personen [BRP]) to identify their vital status and most recent address. All survivors confirmed alive and with a known address in the Netherlands were eligible for invitation. Survivors who were lost to follow-up, living abroad, objected to participate in any scientific research, or who were considered ineligible to participate by their late effects physician (e.g., on active cancer treatment) were excluded.

2.1.2 | Siblings and parents

Siblings identified during the LATER 1 study were also invited to participate in the LATER 2 study for selected research questions (for questionnaires and echocardiogram, electrocardiogram, and cardiac biomarkers). Parents of the invited survivors were invited to participate in the psycho-oncology questionnaire study (see also Table S1).

2.1.3 | Invitation process

Within the web-based LATER study database, we developed a tool to support the invitation process and logistics for the outpatient clinical visit based on the specific inclusion and exclusion criteria of the sub-studies during the period February 2016 to February 2020. A personalized study invitation was generated to facilitate the informed consent for participation to all eligible survivors by the outpatient clinic where the survivor was known (Amsterdam University Medical Center [location VUmc], Leiden University Medical Center, Erasmus Medical Center, University Medical Center Groningen, Radboudumc or Princess Máxima Center for Pediatric Oncology). Each of the 16 sub-studies included specific study groups, risk groups based on the characteristics of the survivor, his/her previous childhood cancer diagnosis and treatment, and the center from which he or she participated. A unique feature of the invitation application is that the program assigned each survivor to the appropriate study group for each sub-study. The late effects clinician then checked if there were any clinical or other reasons to not invite the survivor for the whole study or certain sub-studies and if not, approved to send the invitation. If a survivor agreed to participate, study tests were planned in combination with an already planned outpatient visit. If a survivor did not respond to the initial invitation, the local center sent a reminder or attempted to establish contact with the survivor by phone. To optimize and standardize information for all study centers, manuals were developed concerning the logistics, data collection procedure, and storage of material. The study protocol for all LATER 2 sub-studies was approved by the medical ethics boards of all participating centers.

2.2 | Data collection

For all 6165 five-year childhood cancer survivors in the underlying LATER cohort, detailed information on childhood cancer diagnosis and treatment for the primary cancer and all recurrences was collected from the historic medical records, prior to this study.[7] The overall concept of data collection for the LATER 2 study is summarized in Tables S2 and S3, and alluded to below.

2.2.1 | Physical examination

During the outpatient clinic visit, for both survivors and their siblings, we collected data on height, sitting height, weight, waist circumference, hip circumference, blood pressure (three measurements, of which the last two were registered), and pulse. In addition, among survivors we assessed pubertal stage (in survivors <18 years of age), a skin examination was performed, as well as thyroid palpation, and an assessment of testicular volume among males.

2.2.2 | Clinical tests

In the LATER 2 study, participating survivors were invited for a number of clinical tests, the extent of which was based on age, sex, prior treatment, and participating center. In total, a maximum of seven clinical tests targeting different health outcomes/organ systems were performed, including dual-energy x-ray absorptiometry (DXA) scan, echocardiogram, electrocardiogram, 6-minute walking test, hand-grip

test, pulmonary function test, and 24-hour blood pressure measurements. Siblings of survivors who underwent echocardiogram and electrocardiogram measurements were invited to also undergo echocardiogram and electrocardiogram, to control, to some extent, for genetic predispositions. In case of multiple siblings, the sibling with the same sex and closest in age to the corresponding survivor was invited.

2.2.3 | Questionnaires

Participating survivors and siblings were asked to complete a questionnaire on general health and lifestyle. Because survivors and siblings who participated in the LATER 1 questionnaire study in 2012–2014[7] already filled out extensive data on health and lifestyle, those persons were only asked to complete a short repeat version of this questionnaire focusing on main health outcomes only (Table S3). Survivors and siblings who did not participate in the LATER 1 questionnaire study were asked to complete the full questionnaire on general health and lifestyle (Table S3). Several other outcomes were assessed with, mostly validated, questionnaires (Table S4). Each survivor was invited to complete outcome-specific questionnaires for sub-studies for which the survivor was eligible. Questionnaires were spread in time (questionnaires on physical limitations were given before and during the outpatient clinic recruitment visits, and questionnaires on psychosocial and psychosexual topics were given after the visit) in order to limit the burden for survivors. Siblings of survivors also received questionnaires on psychosocial outcomes, fatigue, and skin health, and parents of survivors received questionnaires on psychosocial outcomes.

2.2.4 | Bio-material

To obtain deoxyribonucleic acid (DNA), a blood or saliva sample was collected, DNA was extracted and stored in the LATER study biobank. Additional blood samples were drawn from survivors and siblings and stored in −80°C in several aliquots for study questions and future central analyses. For specific outcomes (renal and splenic function), blood was analyzed directly in the lab of the local center. For some sub-studies, we also collected a semen specimen, urine sample, and saliva sample.

2.3 | Monitoring of the quality of study participation and communication

The LATER Central Office developed an extensive data and procedural monitoring program on informed consent procedures and documentation as well as data registration, which started after the inclusion of the first two survivors per center. Annual monitor visits were held at each center. For the monitor visit, a standard operational procedure was made, which included checks for correct use of inclusion criteria, the informed consent procedure, and data entry. After the visit, a monitor visit report was made. This report entailed a summary of the findings, recommendations for improvement, and a list of actions to be resolved. Inclusion rates for all centers and all sub-studies were calculated and visualized quarterly, to monitor sub-study inclusions and to allow for comparison with predefined targets. Based on these data, a study group of a sub-study was closed when a respective study group reached the predefined target number. In addition to the annual site monitoring, the Central LATER office implemented ongoing monitoring on selected items and activities in all centers, in order to facilitate local sites to continuously improve data quality.

2.4 | Statistical analyses current paper

In the current paper, we compared the participants and nonparticipants by sex, age at diagnosis, type of cancer, attained age (age at invitation), follow-up time since childhood cancer diagnosis until invitation, and for cancer treatment (dichotomous variables for any chemotherapy, any radiotherapy, any surgery, and categorical variable for bone marrow/stem cell transplant [no, autologous, allogenic, unknown]). Treatment variables represent cumulative exposures accumulated during treatment for primary tumor, metastases, and recurrences, regardless of time since first diagnosis, and captured from original medical files in the treatment centers.[7] Differences in the distributions were tested using a chi-square test.

3 | RESULTS

3.1 | Characterization of participants

In Figure 2, the recruitment process is summarized. Of the underlying cohort of 6165, 611 survivors died and 401 survivors refused participation in any scientific research prior to October 10, 2016. Thus, for the LATER 2 study, we started with 5153 potentially eligible survivors. After careful tracing and assessment, we excluded 418 individuals for the following reasons: 99 survivors died between the recruitment periods of the LATER 1 and LATER 2 study, 55 survivors were lost to follow-up, 179 survivors were living abroad, 47 survivors were considered ineligible for participation in the LATER 2 study by their physician, and 38 individuals were not invited due to other reasons (e.g., not proficient in Dutch language, administrative errors in the invitation process). In all, 4735 survivors were invited for the LATER 2 study. In total, 2519 (53.2%) of eligible survivors participated in the study, 744 survivors declined participation, 1472 survivors did not respond to the first invitation and all reminders. Of the participating survivors, 127 signed the informed consent, but eventually did not participate in additional data collection for the study. For this group, we were able to extract data from the medical records from their regular late effects outpatient clinic visit and used this for some of the research questions in the study.

In Figure 3, the planned and realized trend-lines of invitation and outpatient clinic visit are shown. Although the participation rate was initially lower than expected, we eventually included our intended number of 2500 survivors. In addition, 541 (36.1%) of 1499 invited

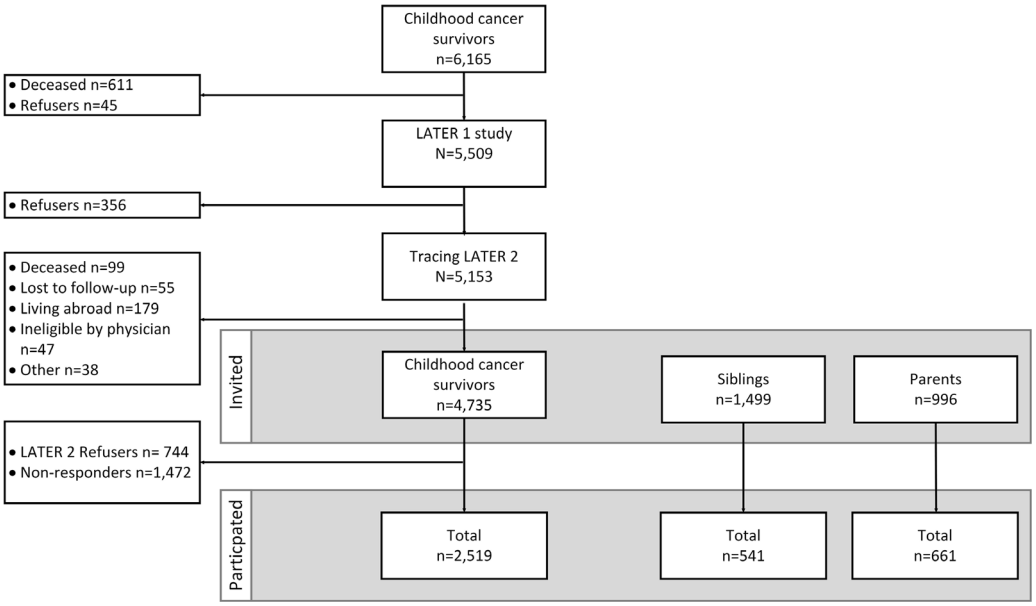

FIGURE 2 Flowchart of invitation process and participation of survivors, siblings, and parents in the Dutch Childhood Cancer Survivor Study (DCCSS) LATER 2 study

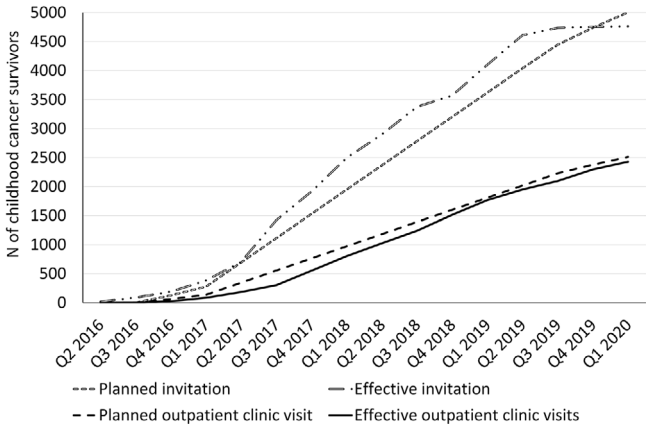

FIGURE 3 The planned and realized trend-lines of invitation and outpatient clinic visit

siblings and 661 (66.4%) of 996 invited parents participated in the LATER 2 study.

Table 1 presents demographic information, tumor characteristics, treatment, and follow-up information of the survivors in the LATER 2 study. Of the 2519 participating survivors, 49.3% were female (n = 1242). Median follow-up time since childhood cancer diagnosis was 26.9 years (range 14.8–54.7 years) and median attained age was 34.4 years (range 15.4–66.6 years). The majority of the participating survivors had been diagnosed with leukemia, myeloproliferative disease and myelodysplastic disease (35.6%), lymphoma and/or reticuloendothelial neoplasm (18.9%), and renal tumor (11.3%). For treatment of primary cancer or recurrences, 13 (0.5%) survivors did not have any recorded surgery, chemotherapy, or radiotherapy (mainly neuroblastoma stage 4S and low-grade CNS tumors, which sometimes have a wait-and-see policy), 163 (6.5%) survivors received surgery only, 1375 (54.6%) survivors received chemotherapy (with or without surgery), 133 (5.3%) survivors received radiotherapy (with or without surgery), and 834 (33.1%) survivors received both chemotherapy and radiotherapy (with or without surgery). Of participating survivors, 166 (6.6%) had received a hematopoietic stem cell transplant, of which 57 (2.3%) were autologous and 109 (4.3%) were allogenic. When comparing participants with nonparticipants (Table 1) in univariate analyses, we observed that females were more likely to participate than males ($p < .00001$), CNS survivors were less likely to participate compared to other cancer types ($p < .00001$), and survivors treated with chemotherapy and radiotherapy were more likely and those treated with surgery only were less likely to participate compared to other survivors.

3.2 | Clinical tests, questionnaires, and bio-materials

In Table 2, the numbers of participants who underwent specific clinical tests are displayed.

The following clinical tests were performed: 104 24-hour blood pressure measurements, 311 6-minute walk tests, 1657 DXA scans, 1352 echocardiograms, 1385 electrocardiograms, 1816 hand-grip tests, and 586 pulmonary function tests. The LATER questionnaire was completed by 2229 survivors (n = 473 full/n = 1756 short repeat questionnaire; see Methods section for explanation). The following biomaterials were obtained: 2257 blood samples, 271 saliva specimens, 657 semen specimens, 979 urine samples. In total, we extracted DNA for 2270 survivors, that is, 90.1% of all participating survivors. Among siblings, we collected 277 echocardiograms, 272 electrocardiograms, and 278 blood samples.

TABLE 1 Baseline characteristics of DCCSS LATER cohort

Characteristics	Underlying cohort ($n = 6165$)		invited study population ($n = 4735$) (76.8% of underlying cohort)		Participants ($n = 2519$) (53.2% of the invited population)		Nonparticipants ($n = 2216$) (46.8% of the invited population)		*p*-Value participants vs. nonparticipants
	n	%	*n*	%	*n*	%	*n*	%	
Sex									<.00001
Female	2731	44.3%	2092	44.2%	1242	49.3%	850	38.4%	
Male	3433	55.7%	2643	55.8%	1277	50.7%	1365	61.6%	
Transgender	1	0.01%	0	0.0%	0	0.0%	1	0.05%	
Primary childhood cancer (ICCC-3)									<.00001
Leukemias, myeloprofiferative diseases, and myelodysplastic diseases	2094	34.0%	1631	34.4%	897	35.6%	734	33.1%	.07
Lymphomas and reticuloendothelial neoplasms	1062	17.2%	865	18.3%	477	18.9%	388	17.5%	.21
CNS and miscellaneous intracranial and intraspinal neoplasms	844	13.7%	560	11.8%	232	9.2%	328	14.8%	<.00001
Neuroblastoma and other peripheral nervous cell tumors	324	5.3%	256	5.4%	151	6.0%	105	4.7%	.06
Retinoblastoma	33	0.5%	26	0.5%	11	0.4%	15	0.7%	.26
Renal tumors	596	9.7%	497	10.5%	284	11.3%	213	9.6%	.06
Hepatic tumors	52	0.8%	48	1.0%	21	0.8%	27	1.2%	.19
Bone tumors	370	6.0%	262	5.5%	139	5.5%	123	5.6%	.96
Soft tissue and other extraosseous sarcomas	450	7.3%	339	7.2%	181	7.2%	158	7.1%	.94
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	232	3.8%	180	3.8%	90	3.6%	90	4.1%	.39
Other malignant epithelial neoplasms and malignant melanomas	102	1.7%	66	1.4%	32	1.3%	34	1.5%	.44
Other and unspecified malignant neoplasms	6	0.1%	5	0.1%	4	0.2%	1	0.0%	.23
Age at diagnosis (years)	*5.6*	*0–17.9*			*5.4*	*0–17.4*	*5.4*	*0–17.7*	.80
0–4	2727	44.2%	2208	46.6%	1184	47.0%	1024	46.2%	
5–9	1628	26.4%	1281	27.1%	677	26.9%	604	27.3%	
10–14	1285	20.8%	970	20.5%	508	20.2%	462	20.8%	
15–17	376	6.1%	271	5.7%	150	6.0%	121	5.5%	
Treatment period									.51
1963–1969	119	1.9%	67	1.4%	35	1.4%	32	1.4%	
1970–1979	978	15.9%	628	13.3%	336	13.3%	292	13.2%	
1980–1989	1931	31.3%	1454	30.7%	781	31.0%	673	30.4%	
1990–2001	3137	50.9%	2586	54.6%	1367	54.3%	1291	58.3%	
Age at invitation (years)					*34.2*	*15.5–65.4*	*34.4*	*15.4–66.6*	.35
<18	–	–	49	1.0%	36	1.4%	13	0.6%	
18–30	–	–	1313	27.7%	821	32.6%	492	22.2%	
30–40	–	–	1511	31.9%	944	37.5%	567	25.6%	
>40	–	–	1118	23.6%	718	28.5%	400	18.1%	

(Continues)

TABLE 1 (Continued)

Characteristics	Underlying cohort ($n = 6165$)		invited study population ($n = 4735$) (76.8% of underlying cohort)		Participants ($n = 2519$) (53.2% of the invited population)		Nonparticipants ($n = 2216$) (46.8% of the invited population)		p-Value participants vs. nonparticipants
	n	%	*n*	%	*n*	%	*n*	%	
Follow-up time since childhood cancer diagnosis to invitation					26.9	14.8–54.7	26.8	13.2–55.9	.53
10–20	–	–	696	14.7%	531	21.1%	438	19.8%	
20–30	–	–	1896	40.0%	989	39.3%	907	40.9%	
30–40	–	–	1373	29.0%	741	29.4%	632	28.5%	
40–50	–	–	452	9.5%	232	9.2%	220	9.9%	
50–60	–	–	45	1.0%	26	1.0%	19	0.9%	
Chemotherapy[a]									<.00001
No	1123	18.2%	793	16.7%	309	12.3%	484	21.8%	
Yes	5005	81.2%	3935	83.1%	2210	87.7%	1725	77.8%	
Missing	37	0.6%	7	0.1%	0	0.0%	7	0.3%	
Radiotherapy[a]									.0002
No	3608	58.5%	3026	63.9%	1551	61.6%	1475	66.6%	
Yes	2527	41.0%	1701	35.9%	967	38.4%	734	33.1%	
Missing	30	0.5%	8	0.2%	1	0.0%	7	0.3%	
Surgery[a]									.008
No	2912	47.2%	2316	48.9%	1280	50.8%	1036	46.8%	
Yes	3185	51.7%	2396	50.6%	1232	48.9%	1164	52.5%	
Missing	68	1.1%	23	0.5%	7	0.3%	16	0.7%	
Hematopoietic cell transplantion[a,b]									.0005
No	5532	92.0%	4445	93.9%	2337	92.8%	2108	95.1%	
Autologous transplant	155	2.6%	91	1.9%	57	2.3%	34	1.5%	
Allogenic transplant	231	3.8%	161	3.4%	109	4.3%	52	2.3%	
Missing	98	1.6%	33	0.7%	16	0.6%	17	0.8%	
Therapy									<.00001
No treatment	61	1.0%	39	0.8%	13	0.5%	26	1.2%	.012
Surgery only	575	9.3%	453	9.6%	163	6.5%	290	13.1%	<.00001
Chemotherapy ± surgery	2967	48.1%	2533	53.5%	1375	54.6%	1158	52.3%	.007
Radiotherapy ± surgery	484	7.9%	300	6.3%	133	5.3%	167	7.5%	.001
Chemotherapy and radiotherapy ± surgery	2030	32.9%	1400	29.6%	834	33.1%	566	25.5%	<.00001
Missing	48	0.8%	10	0.2%	1	0.0%	9	0.4%	.006

Abbreviations: DCCSS, Dutch Childhood Cancer Survivor Study; ICCC-3, International Classification of Childhood Cancer, Third edition.

[a]For primary cancer and recurrences.

[b]Only for $n = 6016$ childhood cancer survivors (all survivors who did not decline registration in the DCCSS LATER database).

4 | DISCUSSION

In this paper, we describe the methodology, participation rates, and data availability of the DCCSS LATER 2 study. With the clinical data collected in the LATER 2 study, we will be able to fill gaps in knowledge that have been identified in the published recommendations of the International Guideline Harmonization Group (IGHG).[8]

The LATER 2 study collected extensive data on clinical outcomes and questionnaires for 2519 childhood cancer survivors, 632 siblings, and 580 parents. The data collection was finished in 2020. An important strength of our study is that we evaluated objective clinical outcomes by clinical tests using blood and urine samples in combination with functional tests, and therefore do not rely solely on self-reported outcomes, which can be prone to recall bias. Another strength is that we used mostly validated questionnaires for our out-

TABLE 2 Clinical tests for the different outcomes, and the number of childhood cancer survivors and siblings having participated in the tests

Childhood cancer survivors		
Diagnostic test	**Outcome**	**Participated (*n*)**
LATER questionnaire (general, shortened)	General	2229
DNA	General	2270
Blood	Several outcomes[a]	2257
Saliva	Xerostomia	271
Semen	Male fertility	657
Urine	Renal function	979
DXA scan	Bone health, metabolic syndrome, lifestyle/aging	1657
24-Hour blood pressure measurement	Renal function	104
6-Minute walk test	Bone health, metabolic syndrome, lifestyle/aging	311
Echocardiogram	Cardiac function	1352
Electrocardiogram	Cardiac function	1385
Hand-grip test	Bone health, metabolic syndrome, lifestyle/aging	1816
Lung function test	Pulmonary function	586
Siblings		
Diagnostic test	**Outcome**	***n***
Blood	Cardiac function	278
Echocardiogram	Cardiac function	277
Electrocardiogram	Cardiac function	272

[a]Bone health, cardiac function, fatigue, growth hormone, lifestyle/aging, male fertility, metabolic syndrome, psychosexuality, pulmonary function, renal function, skin health, spleen function, and thyroid function.

comes. Furthermore, by including siblings for some outcomes, we will be able to compare prevalence of outcomes to a control group. The availability of detailed information on childhood cancer diagnosis and treatment enables indepth analyses on potential risk factors for clinical outcomes.

In the LATER 2 study, there is a risk of participation bias, as we found some differences between participants and nonparticipants in sex, type of cancer (e.g., CNS tumor survivors were less likely to participate), hence also in childhood cancer treatment. This might under- or overestimate the prevalence of health outcomes. The consequences of these differences may vary between outcome-specific sub-studies. Therefore, differences between the participants and nonparticipants will be tested for each sub-study to evaluate specific patterns of potential participation bias specific to the health outcomes evaluated. If there are differences that are important for the specific research questions, controlling for covariates associated with selection, inverse probability weighting, and/or sensitivity analysis will be considered. Furthermore, there is risk of survival bias, as those who were affected with the most serious outcomes might have passed away and therefore did not participate in this study.

The collected clinical data will be a repository for future studies. After completion of the primary studies on the a priori-defined clinically relevant research questions, we will combine data from different sub-studies, for example, metabolic syndrome and cardiac diseases and quality of life related to medical outcomes, to answer further questions, which may also include health outcomes ascertained using record linkage in the LATER 1 study (e.g., benign and malignant tumors). In the future, it will also be possible to link clinical parameters measured during the LATER 2 study to health outcomes that occur later.

The current study is one of the largest clinical studies among childhood cancer survivors and includes a large variety of clinical outcome data collected in all types of childhood cancer survivors. As far as we are aware, the St. Jude Lifetime Cohort Study (SJLIFE) represents the only other endeavor of this scale covering the full spectrum of childhood cancer types in which the burden of clinical outcomes is ascertained during a clinical visit.[9] Because we collected a lot of similar data to SJLIFE, this can stimulate future collaboration, such as pooling data or serving as validation cohort for each other. However, we also collected unique data, which were not collected in the SJLIFE study so far, for example, data on hypo salivation/xerostomia. Currently, the Swiss Childhood Cancer Survivor Study also has an ongoing effort of collecting clinical outcome data.[10] Future collaboration will be important to improve knowledge on rare health outcomes.

In summary, in the LATER 2 study, extensive information on various clinical and physical and psychosocial health outcomes has been assessed during an outpatient clinic visit in a large group of childhood cancer survivors. The high-quality data will provide valuable insights into risks of and risk factors for clinical and physical and psychosocial health outcomes and factors for early recognition of health outcomes in long-term childhood cancer survivors. With this information, we

will contribute to reducing important gaps in knowledge, and finally improve the quality of life and care for childhood cancer survivors.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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