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CLINICAL RESEARCH
Prevention and epidemiology

Burden of cardiovascular risk factors and cardiovascular disease in childhood cancer survivors: data from the German CVSS-study

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Aims The **c**ardiac and **v**ascular late **s**equelae in long-term **s**urvivors of childhood cancer (CVSS)-study aimed to quantify the prevalence of cardiovascular risk factors (CVRF) and cardiovascular disease (CVD) in German childhood cancer survivors (CCS).

Methods and results In the CVSS-study (NCT02181049), 1002 CCS (age range 23–48 years) diagnosed with neoplasia prior to 15 years of age between 1980 and 1990 prospectively underwent a systematic, standardized clinical and laboratory cardiovascular screening, identical to the population-based Gutenberg Health Study (GHS) cohort. For 951 individuals, prevalences of CVRF and CVD were primarily compared to the GHS sample and to two further German population-based cohorts. Using log-binomial regression models, an increased risk for occurrence of arterial hypertension [relative risk (RR) 1.38, 95% confidence interval (95% CI 1.21–1.57)] and dyslipidaemia [RR 1.26 (95% CI 1.12–1.42)] was found. This indicates a premature occurrence compared to the general population of approximately 6 and 8 years, respectively [rate advancement period estimator, $RAP_{hypertension}$ 5.75 (95% CI 3.5–8.0) and $RAP_{dyslipidaemia}$ 8.16 (95% CI 4.4–11.9)]. Overall, no differences were observed for obesity and diabetes. Overt CVD was present in 4.5% (95% CI 3.0–6.6%) of CCS [RR 1.89 (95% CI 1.34–2.66), RAP_{CVD} 7.9 (95% CI 4.1–11.7)], of which the most frequent entities were congestive heart failure and venous thromboembolism. Prevalences of CVRF and CVD increased with age without reaching a plateau over time.

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Conclusion This large CCS screening examination revealed consistently in comparison to three population samples a considerably increased risk for premature CVD. The findings in these young adult CCS indicate a high burden of cardiovascular morbidity and mortality in the long term.

Clinicaltrials.gov-Nr NCT02181049.

Keywords Cardiotoxicity • Long-term survivors • Late sequelae • Cardiovascular morbidity • Cardio-oncology

Introduction

Since treatment of childhood cancer has improved significantly in the last decades with an average overall survival above 80%,[1] adverse late effects among long-term childhood cancer survivors (CCS) have become increasingly important. Currently, about 33 000 long-term CCS are followed by the German Childhood Cancer Registry (GCCR).[1] Cardiovascular disease (CVD) is the most common non-neoplastic cause of premature mortality in this population.[2] Most studies primarily obtained data with regard to cardiac or vascular toxicity, based on questionnaires, hospital admission data, or death certificates and frequently lacked a control cohort.[2–8] Only few study groups have directly assessed the comprehensive cardiovascular status of CCS through clinical and laboratory examinations.[9–11] Hence, data from large-scale and highly standardized examination studies are needed to extend valid evidence in this field and to help refining current recommendations on management of cardiovascular toxicity in CCS, as recently provided by the European Society of Cardiology.[12,13] The **c**ardiac and **v**ascular late **s**equelae in long-term **s**urvivors of childhood cancer (CVSS)-study was designed to identify cardiovascular risk factors (CVRF) as well as subclinical and clinical CVD by state-of-the-art phenotyping in German CCS and to evaluate their association with oncologic disease, cancer treatment, and genetics. Aiming to quantify cardiovascular burden in CCS, prevalences of traditional CVRF and CVD were analysed and compared to data from three population-based samples.

Methods

Participants

German CCS were eligible for participation in the CVSS-study when diagnosed with a neoplasia according to the International Classification of Childhood Cancer (ICCC3),[14] prior to 15 years of age, between 1980 and 1990, registered at the GCCR, survived more than 5 years after initial cancer diagnosis and received antineoplastic treatment at one of 34 paediatric cancer centres participating in the CVSS-study. Survivors of Hodgkin lymphoma and a small proportion of former nephroblastoma patients (diagnosed in 1990) were not considered, since they were included in other investigations.

Among 2894 invited CCS, 1002 individuals were examined between October 2013 and February 2016 in the study centre at the University Medical Center Mainz. The CVSS-study participants underwent a highly standardized clinical evaluation over 5.5 h at the Gutenberg Health Study (GHS) cardiovascular examination platform[15] (see also section 'Population-based cohort samples'). All procedures performed in this study were in accordance with the ethics standards of the institutional research committee (approved by ethics review committee of Rhineland-Palatinate Chamber of Physicians) and with the Declaration of Helsinki. All participants gave written informed consent for study participation and treatment data retrieval.

Acquisition of medical data

Information on medical history was collected through a computer-assisted personal interview (CAPI) and, if available, from medical records. Cancer- and treatment-related data were abstracted either from primary health records of former treating medical centres and/or the centrally documented individual therapy data at the respective study centres of the Society for Paediatric Oncology and Haematology (GPOH) and validated by trained medical staff.

Assessment of cardiovascular risk factors, cardiovascular disease, and medication

The following CVRF were recorded: arterial hypertension (in the following termed 'hypertension'), dyslipidaemia, obesity, diabetes mellitus (in the following termed diabetes), smoking, and positive family history for myocardial infarction and/or stroke. The assessment of CVRF was performed through a CAPI and clinical and laboratory examinations. The definition of the CVRF is summarized in Supplementary material online, *Table S1*.

The following data on CVD were assessed by a CAPI, when diagnosed by a physician and, if possible, ascertained by medical records: congestive heart failure (CHF) (requiring medication in the last 12 months), coronary heart disease including myocardial infarction, stroke, peripheral artery disease, atrial fibrillation, and venous thromboembolism (VTE) including deep venous thrombosis and pulmonary embolism. The participants' current drug intake was assessed by means of CAPI and evaluation of provided medication packages and categorized according to the Anatomical Therapeutic Chemical classification system of the World Health Organization Collaborating Centre for Drug Statistics Methodology.

Population-based control cohorts

Prevalence of CVRF and CVD in the CVSS-study sample was compared to the GHS population sample as cardiovascular data was obtained by identical standardized examinations. The GHS is a population-based, prospective, observational, single-centre cohort, including over 15 000 participants from the general population of Mainz and Mainz-Bingen, aiming to evaluate and improve cardiovascular risk stratification.[15] Additionally, for harmonized and thus comparable variables, age-adapted study samples from two further German population-based cohort studies, the German Health Interview and Examination Survey for Adults (DEGS) (2008–2011) and the Cooperative Health Research in the region of Augsburg (KORA) (S4), were selected for comparison.[16,17]

Statistical analysis

Descriptive measures were calculated for demographic, clinical, and treatment variables. Absolute and relative frequencies for CVRF and CVD were computed according to ICCC3 diagnoses and sex. Indirect standardizations were carried out to provide comparability in terms of age and sex: data from samples of three population-based cohort studies were weighted with age and sex distribution of the CVSS-study cohort. For comparison with the GHS cohort, only the subsets with an overlapping age range (35–48 years) were analysed. Standardized prevalence ratios (prevalence of the event in the CVSS/weighted prevalence of the event in the comparison cohort) were calculated and non-parametric bootstraps with replacement ($n = 1000$ random samples of the observed data) were carried out to estimate 95% confidence limits.[18] A log-binomial regression approach was used to analyse the impact of 'childhood-cancer' (independent variable) on CVRF and CVD (dependent variables) compared to the reference GHS cohort, which is appropriate to model relative risk (RR) directly. Relative risks were presented with 95% confidence intervals (CI). The prevalence estimated by the regression model was plotted with the observed prevalence in 5-year age categories. The rate advancement period estimator (RAP) with the asymptotic 95% CI was calculated to estimate the extent of prematurity of CVRF/CVD in the CVSS sample.[19,20] Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and Software R (Version 3.4.0, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Among 1002 examined participants, 951 individuals were analysed, as CCS with subsequent neoplasia ($n = 51$) were excluded. The CVSS-study sample comprised 425 (44.7%) female and 526 (55.3%) male participants with a mean age of 6.1 years (range 0–14) at initial childhood cancer diagnosis and 34.0 years (range 23–48) at follow-up, respectively. Mean time from diagnosis to examination was 28.4 years (range 23–36). More than half of the examined CVSS-study participants had been previously diagnosed with leukaemia or lymphoma (53.4%, $n = 508$). Antineoplastic treatment-related data were obtained and validated for 91.9% ($n = 874$) of CVSS-study participants. The majority (91.1%, $n = 796$) had received either chemo- or radiotherapy. Demographic, diagnostic, and treatment characteristics of the CVSS-study sample are shown in *Table 1*. Demographic data for the CVSS-study, GHS, DEGS, and KORA samples are presented in Supplementary material online, *Table S2*.

Table 1 Demographic, diagnostic and treatment characteristics of CVSS-study participants ($n = 951$)

	CVSS % (*n*)
Sex	
Female	44.7 (425)
ICCC3 diagnosis	
Leukaemia	43.5 (414)
Central nervous system tumours	12.8 (122)
Lymphoma	9.9 (94)
Renal tumours	8.1 (77)
Sympathetic nervous system tumours	7.6 (72)
Soft tissue sarcomas	7.5 (71)
Malignant bone tumours	5.3 (50)
Germ cell tumours	2.7 (26)
Retinoblastoma	1.1 (10)
Hepatic tumours	0.7 (7)
Carcinoma	0.7 (7)
Other	0.1 (1)
Age at diagnosis (years)	
<1	9.45 (90)
1–<4	30.8 (293)
4–<8	27.7 (263)
8–<11	13.5 (128)
11–<15	18.6 (177)
Follow-up time (years)	
20–<25	16 (152)
25–<30	50.8 (483)
30–<35	32.0 (304)
35–<40	1.3 (12)
Treatment	
Chemotherapy and radiation	50.8 (444)
Chemotherapy only	37.2 (325)
Radiation only	3.1 (27)
No chemotherapy, no radiation	8.5 (74)
Radiation unknown	0.5 (4)

Treatment data were available in 91.9% ($n = 874$).
CVSS, **c**ardiac and **v**ascular late **s**equelae in long-term **s**urvivors of childhood cancer; ICCC3, International Classification of Childhood Cancer.

Prevalence of cardiovascular risk factors

The highest prevalences of CVRF within the CVSS-study sample were identified for hypertension (23.0%) and dyslipidaemia (28.3%), whereas a low frequency was recorded for diabetes (2.0%) (*Table 2* and Supplementary material online, *Table S3*). Compared to GHS participants, CVSS-study participants had an age-adjusted 38% increase in risk for hypertension [RR 1.38 (95% CI 1.21–1.57)] and a 26% increase in risk for dyslipidaemia [RR 1.26 (95% CI 1.12–1.42)]. The calculation of RAP indicated that in CVSS-study participants, hypertension and dyslipidaemia occurred approximately 6 years [RAP 5.75 (95% CI 3.5–8.0)] and 8 years [RAP 8.16 (95% CI 4.4–11.9)] prior to GHS participants. We did not reveal any difference between the CVSS-study and the GHS population sample for the prevalence of diabetes and obesity. Regression models estimated for both, CVSS-study and GHS participants, a continuously increasing probability to suffer from hypertension, dyslipidaemia, obesity, and diabetes with age, without reaching a plateau. Hence, 17.1% and 24.7% of the CVSS-study participants were estimated to have hypertension and dyslipidaemia, respectively, by age 30 years, increasing to 39.3% and 38.0% by age 45 (*Figure 1*). Relative risk estimates were mainly confirmed by the standardized prevalence ratios, which were derived from the age-adapted (35–48 years) CVSS-study and GHS sample (*Table 3*).

The CVSS-study sample contained the lowest proportion of smokers of all four study cohorts. With regard to positive family history for myocardial infarction/stroke, similar relative frequencies were obtained in all comparable study samples with the exception of KORA. Here, the prevalence was slightly lower in the CVSS-study

Table 2 Prevalence of cardiovascular risk factors, cardiovascular diseases, other chronic diseases and drug intake among CVSS-study participants ($n = 951$)

	CVSS % (*n*)
Cardiovascular risk factor	
Dyslipidaemia	28.3 (269)[b]
Arterial hypertension	23.0 (219)[b]
Smoking	21.5 (204)[b]
Obesity	17.4 (165)
Positive family history for myocardial infarction/stroke	19.7 (187)[c]
Diabetes mellitus	2.0 (19)
Metabolic syndrome	16.9 (161)
Cardiovascular disease[a]	4.5 (43)[d]
Venous thromboembolism	2.0 (19)[b]
Congestive heart failure	1.2 (11)[b]
Stroke	0.5 (5)[b]
Peripheral artery disease	0.5 (5)[b]
Atrial fibrillation	0.4 (4)[b]
Coronary heart disease	0.3 (3)[b]
Other chronic diseases	
Autoimmune disease	3.8 (36)[b]
Chronic obstructive pulmonary disease	2.9 (28)[b]
Chronic kidney disease	1.6 (15)[b]
Chronic liver disease	0.5 (5)[b]
Intake of drugs	
Any drug intake	69.3 (659)[b]
Cardiovascular system	11.0 (105)[b]

CVSS, cardiac, and vascular late sequelae in long-term survivors of childhood cancer.
[a]At least one of the reported cardiovascular diseases.
[b]<1% missings.
[c]<10% missings.
[d]<5% missings.

cohort. For hypertension and dyslipidaemia, the comparison with DEGS confirmed the abovementioned findings. However, compared to KORA prevalences for hypertension as wells as for obesity and diabetes were higher in the CVSS-study sample (*Table 4*).

Within the CVSS-study, hypertension was highly prevalent in former patients with malignant bone tumours (42%, $n = 21$) and soft tissue sarcomas (36.6%, $n = 26$). For dyslipidaemia, a markedly elevated prevalence was observed in survivors of lymphoma (42.6%, $n = 40$). For both, hypertension and dyslipidaemia, prevalence was considerably increased for male CVSS-study participants compared to females (Supplementary material online, *Table S4*).

Prevalence of cardiovascular disease and medication intake

At least one of the CVDs was prevalent in 4.5% [(95% CI 3.0–6.6%), $n = 43$] of CVSS-study participants. Of interest, 31 of 43 individuals were below 40 years of age. Congestive heart failure (1.2%; $n = 11$) and VTE (2.0%; $n = 19$) accounted for 64% of all documented CVDs. Coronary heart disease, stroke, peripheral artery disease, and atrial fibrillation were reported by 0.3%, 0.5%, 0.5%, and 0.4% of CVSS-study participants, respectively (*Table 2*). All strokes occurred at least 19 years after diagnosis. According to age-adjusted regression estimates, CVSS-study participants were nearly at a two times elevated risk for CVD [RR 1.89 (95% CI 1.34–2.66)] compared to the GHS cohort. On average, CVSS-study participants developed CVD 7.9 years prior to the GHS sample [RAP 7.9 (95% CI 4.1–11.7)]. In terms of CHF, risk for the CVSS-study sample was estimated to be nearly seven times higher [RR 6.76 (95% CI 2.73–16.72)] than for the GHS cohort. As for the CVRF, probability of CVD and CHF increased considerably with age for the CVSS-study as well as for the GHS sample. In the CVSS-study cohort, probability to develop CVD and CHF respectively was estimated as 2.9% and 0.8% by age of 30 years, increasing to 9.6% and 2.3% by age 45. No plateauing was observed. Again, compared to GHS, RR for the CVSS-study cohort to suffer from CVD and CHF was not changing with age (*Figure 2*). For VTE, age-adjusted RR was calculated with 1.77 (95% CI 1.04–3.01). In comparison to DEGS, CVSS-study participants were estimated to be approximately at a three-fold increased risk for CHF [2.96 (95% CI 1.38–6.34)]. Relative risk was calculated with 2.42 (95% CI 1.13–5.19), when comparing to KORA (*Figure 2*).

Prevalence of CVD, CHF, and VTE tended to be higher in female compared to male CVSS-study participants (Supplementary material online, *Table S4*). With regard to ICCC3 diagnoses, we did not observe any difference neither for CVD nor for CHF or VTE among CVSS-study participants (Supplementary material online, *Table S4*). Consumption of both, any and cardiovascular medication, was more common among CVSS-study participants (69.3% and 11.0%, respectively) than among the DEGS (56.5% and 5.9%, respectively) and KORA (46.5% and 4.2%, respectively) cohorts (*Table 2* and Supplementary material online, *Table S5*). Similar results were observed for the age-overlapping (35–48 years) CVSS-study and GHS cohort (data not shown).

Discussion

This is the first study to (i) evaluate comprehensively the cardiovascular health status of a large representative CCS cohort by means of a systematic and standardized state-of-the-art phenotyping and to (ii) compare prevalences of traditional CVRF and of CVD characteristics with those of the general population. Contrasting with most of the previous studies, the comparison sample was derived from a population-based study (GHS) and underwent identical cardiovascular examinations in the same study centre. To enhance the validity of our results, harmonized variables were compared to samples from two additional population-based cohorts (DEGS and KORA).

We identified a large proportion of CCS with hypertension (23.0%) and dyslipidaemia (28.3%), which was considerably higher than in the general population. Most of the previous large-scale studies in CCS assessed questionnaire-based data on both outcomes, resulting in considerably lower prevalences.[21,22] However, recent methodically comparable studies support our findings.[10,11,23] Mulrooney *et al.* measured hypertension in 23.3% and dyslipidaemia in 61.9% of a large CCS cohort ($n = 1853$) but did not compare data to the general population. In subsequent analyses, prevalences for

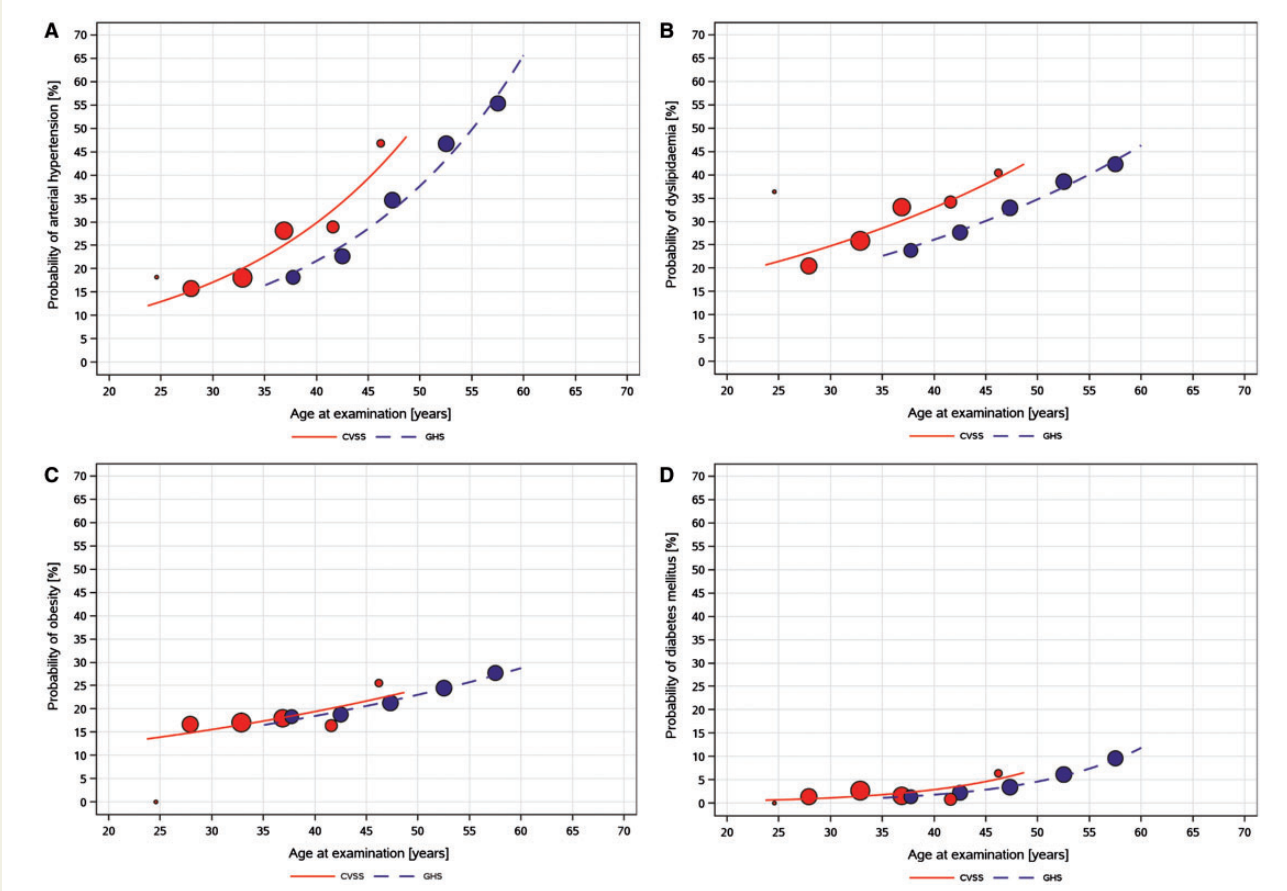

Figure 1 Comparison of cardiovascular risk factors in childhood cancer survivors and the general population: (*A*) arterial hypertension, (*B*) dyslipidaemia, (*C*) obesity, and (*D*) diabetes mellitus. Log-binomial regression analyses from samples of the **c**ardiac and **v**ascular late **s**equelae in long-term **s**urvivors of childhood cancer-study and the Gutenberg Health Study. Circular areas indicate observed prevalences.

hypertension, but not for dyslipidaemia, were recently compared to data from the National Health and Nutrition Examination Survey, estimating similar RR.[23] Thus, to date, the present effort with a total of approximately 14 500 individuals is the largest to provide evidence for a substantially increased prevalence for hypertension and dyslipidaemia in CCS. In this study, survivors of soft tissue sarcoma and malignant bone tumours tended to be at higher risk for hypertension, which is probably attributable to the intensive antineoplastic treatment in these cancer entities. Cancer and its treatment, particularly cardiotoxic chemotherapeutic agents and cardiac directed irradiation, are well recognized to play a major role in the development of CVD.[10,24] Traditional CVRF like hypertension, are assumed to potentiate therapy-associated risk for major cardiac events.[21]

As the analyses primarily aimed to quantify differences in cardiovascular risk between CCS and population samples by assessing the risk factor profile, data were adjusted for the non-modifiable factor age. Since the role of age for present CVD in CCS is ambiguous,[5,7,21,23,25] but age is well recognized to relate with CVD prevalence in the general population,[26] its impact on cardiovascular morbidity was compared between CCS and general population. The data suggest that CVRF and CVD occur prematurely in CCS, and the burden increases markedly with age without reaching a plateau. Notably, the difference in risk compared to the general population seemed not to alter with age. However, most published data indicate an increase of RR for cardiovascular outcome with age, whereas Gudmundsdottir *et al.*[7] conversely revealed a substantial reduction of RR for CVD with increasing age in a large Nordic survivor cohort.[21,23,25] Longitudinal observations over time period are needed to further investigate this issue. We did not find difference for the prevalence of diabetes and obesity between the CVSS-study and the GHS sample. Yet, in comparison with KORA, CVSS-study participants were at elevated risk for both. These inconsistent findings might be explained by regional differences in CVRF prevalence or slightly varying study design and methodology.[28] Research data are congruent regarding obesity, defined by body mass index and implicate no difference in prevalence between CCS and controls,[4,22,27] but inconsistent for diabetes.[4,9,10,21,22] However, CCS may benefit from enhanced clinical attention to both CVRF.

Although frequencies of cardiovascular conditions, particularly for coronary heart disease, stroke, atrial fibrillation, and peripheral artery disease were rare, we found an almost two-fold elevated risk and a

Table 3 Prevalence of cardiovascular risk factors among CVSS and GHS samples after weighing for the age and sex distribution of the CVSS sample

Comparison of CVSS with GHS	Prevalence (%)		Standardized prevalence ratio (95% CI)
	CVSS (35–48 years) *n* = 425	GHS[a] (35–48 years) *n* = 4711	CVSS vs. GHS
Arterial hypertension	30.4	22.3	**1.36 (1.17, 1.58)**
Dyslipidaemia	33.9	28.2	**1.20 (1.03, 1.37)**
Obesity	18.4	19.4	0.94 (0.74, 1.15)
Diabetes mellitus	1.9	1.9	1.00 (0.39, 1.89)
Smoking	18.1	25.5	**0.71 (0.57, 0.87)**
Positive family history for myocardial infarction/stroke	25.7	28.0	0.92 (0.76, 1.07)

CVSS, **c**ardiac and **v**ascular late **s**equelae in long-term **s**urvivors of childhood cancer; DEGS, German Health Interview and Examination Survey for Adults; GHS, Gutenberg Health Study.
[a]Weighted for sex and age distribution in the CVSS-study sample.
Bold values are standard prevalence ratios whose confidence intervals do not include 1.

Table 4 Prevalence of cardiovascular risk factors among CVSS, DEGS, and KORA samples after weighing for the age and sex distribution of the CVSS sample

Comparison of CVSS with DEGS and KORA	Prevalence (%)			Standardized prevalence ratio (95% CI)	
	CVSS *n* = 951	DEGS[a] *n* = 2534	KORA[a] *n* = 2034	CVSS vs. DEGS	CVSS vs. KORA
Arterial hypertension	23.0	10.2	16.6	**2.25 (1.88, 2.71)**	**1.39 (1.19, 1.60)**
Dyslipidaemia	28.3	23.02	[b]	**1.23 (1.07, 1.39)**[b]	[b]
Obesity	17.4	17.3	13.6	1.01 (0.84, 1.19)	**1.28 (1.06, 1.50)**
Diabetes mellitus	2.0	2.1	1.0	0.95 (0.51, 1.61)	**2.00 (1.08, 3.67)**
Smoking	21.5	38.4	38.0	**0.56 (0.48, 0.63)**	**0.57 (0.49, 0.64)**
Positive family history for myocardial infarction/stroke	19.7	[c]	23.5	[c]	**0.83 (0.71, 0.97)**

CVSS, **c**ardiac and **v**ascular late **s**equelae in long-term **s**urvivors of childhood cancer; DEGS, German Health Interview and Examination Survey for Adults; KORA, Cooperative Health Research in the Augsburg Region.
[a]Weighted for sex and age distribution in the CVSS-study sample.
[b]Data were not available due to non-fasting state in 8.1% (*n* = 206) of the DEGS cohort and for the whole KORA cohort.
[c]Data were not available.

premature onset of CVD in CCS, as reported in several retrospective large-scale studies.[7–9,25,29] Tendency towards higher intake of cardiovascular medication in the CCS cohort further highlights this increased cardiovascular morbidity. In CVSS, CHF and VTE accounted for the majority of CVD, occurring with a considerably elevated risk compared to the general population. Since there is little published data on VTE, this study enhances attention to an important and potentially underestimated cardiovascular condition.[6,7] Although numerous large-scale studies on CHF support our findings,[3,5,6,21] recent echocardiographic data indicated a considerably higher frequency of asymptomatic cardiac dysfunction compared to the earlier reported prevalence in CCS. Elevated burden of hypertension and dyslipidaemia in CVSS-study participants at comparably young age is also strongly predictive for future high cardiovascular morbidity and mortality, as known from the general population.[26]

Limitations

Despite of the unique design of this study, several limitations must be addressed, which support an underestimation of CVD burden: Reported, but not measured CVD in the investigation is potentially subject to non-differential misclassification, although this applies to all cohorts. Assessment of CVD was restricted to the most common cardiovascular conditions, not including valvular and pericardial disease as well as conduction disorders. A survival bias is introduced by not considering individuals who died before examination. Two tumour entities well known to predispose for CVD, especially after irradiation,[7,24,25] were not included (Hodgkin lymphoma survivors) or likely under-represented due to potential disability or severe disease (survivors of central nervous system tumours). In all cohorts, healthy individuals and those with severe cardiovascular conditions might be under-represented.

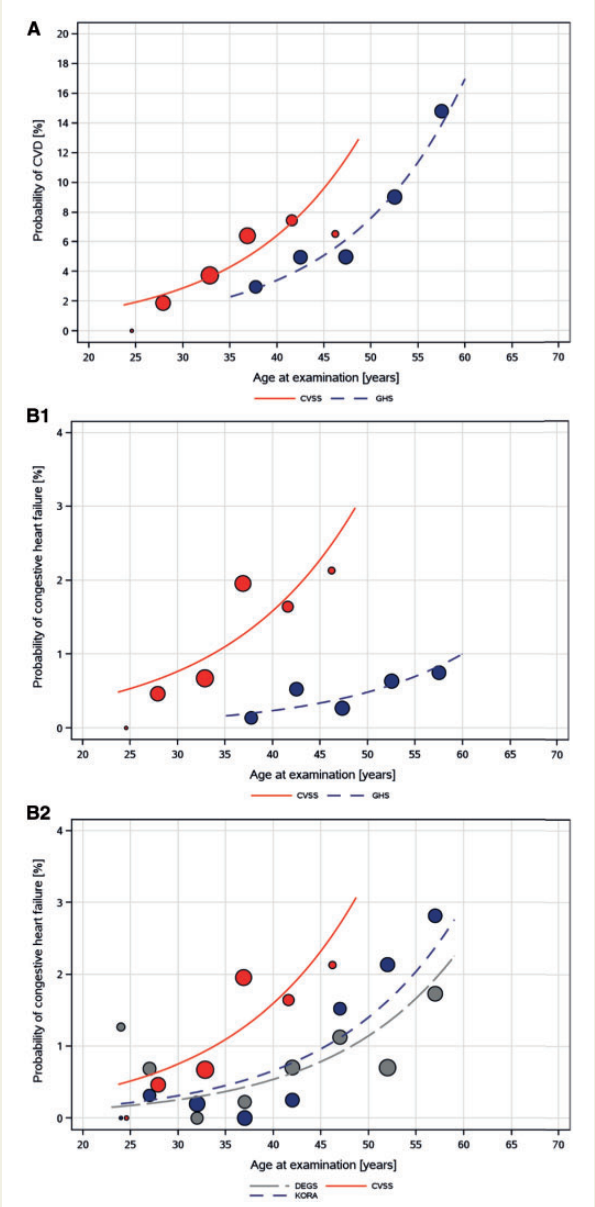

Figure 2 Comparison of cardiovascular disease in childhood cancer survivors and the general population: (*A*) cardiovascular disease, (*B*) congestive heart failure. Log-binomial regression analyses from samples of the **c**ardiac and **v**ascular late **s**equelae in long-term **s**urvivors of childhood cancer-study and (*A*, *B1*) the Gutenberg Health Study and (*B2*) the German Health Interview and Examination Survey for Adults and the Cooperative Health Research in the Augsburg Region. Information on cardiovascular disease was derived from reported data. Circular area indicates observed prevalences.

Future directions

Future research on subclinical CVD (e.g. defined as asymptomatic organ damage[30]) may help to better assess the risk for clinically overt disease and to initiate preventive care. Early focused cardiovascular screening including measurements of blood pressure and lipid profiles should be offered to CCS and not only to high risk subgroups as recommended by current guidelines.[31,32]

Further clinical investigations on CVD in CCS should evaluate (epi-)genetic, proteomic and imaging biomarkers to elucidate pathomechanisms of CVD and to clarify the role of premature aging, since recent data indicate accelerated cellular aging in CCS.[33] This may finally help to develop risk adapted cancer treatment and individualized cardiovascular follow-up care in the sense of precision medicine.

Conclusion

We found a substantially elevated burden of traditional CVRF and CVD in a large German CCS cohort compared to the general population. Cardiovascular disease occurs prematurely and increases with age without reaching a plateau over time. The considerably increased prevalence for hypertension and dyslipidaemia in this young adult CCS indicates a high burden of cardiovascular morbidity and mortality in the long term.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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