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Original Research

Prevalence and determinants of dyslipidemia in 2338 Dutch childhood cancer survivors: a DCCS-LATER 2 study

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Abstract

Objective: Childhood cancer survivors (CCS) face an increased risk of early cardiovascular disease (CVD). In our nationwide CCS cohort, we assessed the prevalence and determinants of dyslipidemia, a well-established risk factor for accelerated atherosclerosis and CVD.

Methods: Prevalence of dyslipidemia was cross-sectionally assessed in 2338 adult CCS and compared to adults with no cancer history (Lifelines, $n = 132\,226$). Dyslipidemia was defined by multiple classifications as well as lipid abnormalities to investigate the impact on prevalence and determinants. Logistic regression models, adjusted for age, sex, and BMI, were used to assess the cohort effect on presence of dyslipidemia. Determinants of dyslipidemia were identified through multivariable logistic regression.

Results: CCS (median age 34.7 year, median follow-up 27.1 year) had significantly increased odds of dyslipidemia compared to the reference cohort according to all classifications (NCEP-ATP-III, WHO, EGIR, CTCAEv.4.03). In survivors without lipid-lowering agents ($n = 2007$), lipid abnormalities were present in 20.6% (triglycerides > 1.7 mmol/L), 30.3% (HDL-c < 1.0/1.3 mmol/L (male/female)), 29.9% (total cholesterol > 5.2 mmol/L), 7.3% (LDL-c > 4.1 mmol/L), and 7.7% (apolipoprotein-B > 130 mg/dL). Compared to references without lipid-lowering agents ($n = 126\,631$), survivors had increased odds of high triglycerides (aOR = 1.89, 95% CI = 1.68-2.13), low HDL-c (aOR = 2.73, 95% CI = 2.46-3.03), and high apolipoprotein-B (aOR = 1.84, 95% CI = 1.53-2.20). Sex, age, BMI, physical activity, abdominal/pelvic, cranial, and total body irradiation, alkylating agents, smoking, growth hormone deficiency, and diabetes mellitus were associated with (≥1 definition of) dyslipidemia in CCS.

Conclusions: CCS is at increased risk of dyslipidemia, with various modifiable and non-modifiable determinants identified, underscoring the importance of survivor-specific risk assessment tools to control cardiovascular morbidity and mortality in this high-risk population.

Keywords: childhood cancer survivor, late adverse effect, dyslipidemia, lipids, atherosclerosis

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Significance statement

In our nationwide childhood cancer survivor (CCS) cohort ($N = 2338$), we show a high prevalence of dyslipidemia (45.3%, NCEP-ATP-III criteria) at a young median age (34.7 year). Our findings underscore the importance of timely lipid status surveillance in CCS at a younger age compared to recommendations in the general population, while many physicians will not be aware of this high risk in young CCS. We show numerous modifiable and non-modifiable determinants (BMI, physical activity, smoking, prior abdominal/pelvic, cranial or total body irradiation, alkylating agents, growth hormone deficiency, and diabetes mellitus) associated with dyslipidemia in CCS, which may be included in survivor-specific risk assessment tools. Early recognition and prevention of dyslipidemia may lead to reduction in subsequent cardiovascular disease and improved outcomes in CCS.

Introduction

Childhood cancer survivors (CCS) face a lifelong increased risk of morbidity and mortality, secondary to their disease and treatment during childhood.[1] Cardiovascular late effects, as well as cardiovascular risk factors (dyslipidemia, diabetes mellitus, and hypertension), are major contributors to this elevated burden of health, as mortality due to coronary and cerebrovascular disease is reported to be up to 12.7 times higher in CCS compared to the general population.[2-4]

Dyslipidemia is often used as a surrogate marker for atherosclerotic cardiovascular disease (CVD), since cumulative exposure to dyslipidemia is associated with accelerated atherosclerosis in the general population.[5] Dyslipidemia is also a component of metabolic syndrome (including hypertriglyceridemia, decreased HDL-c levels, hypertension, abdominal adiposity, and insulin resistance), which is proven to be an important predictor for the development of cerebrovascular and CVD in the general population.[6,7] Recently, the association between dyslipidemia and an increased risk of myocardial infarction and cardiomyopathy in CCS specifically was confirmed as well.[8]

Earlier studies have shown substantial differences in the prevalence of dyslipidemia in CCS,[6] varying between 1.8% and 50.9% (Table 1). Some studies describe CCS to significantly use more lipid-lowering medication compared to their siblings (OR = 1.6, 95% CI = 1.3-2.0),[26] although these results have not been replicated consistently.[15] These differences highlight the heterogeneity in earlier studies, encompassing not only disparities in applied classifications and divergent assessment methods (ie, self-report versus lipid assessment), but differences in demographics and general population risk as well.

Our aim was to assess the prevalence and determinants of dyslipidemia in our nationwide CCS cohort, using extensive lipid level assessments to explore how these outcomes are affected by the application of different lipid abnormalities as well as different classifications of dyslipidemia.

Methods

Study population

This cross-sectional study included data from the nationwide Dutch Childhood Cancer Survivor LATER 2 Study (DCCSS-LATER2).[27,28] The DCCSS-LATER cohort ($n = 6165$) consists of CCS who were diagnosed with childhood cancer (ie, histologically confirmed malignancies or Langerhans cell histiocytosis) < 19 years, were alive ≥5 years after diagnosis, and had been treated in a Dutch pediatric oncology center between 1963 and 2002. For the current study, 4671 adults were invited to participate after they were found eligible, meaning they were still alive and living in the Netherlands in October 2016 and deemed eligible according to their treating physician (Figure S1). The study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Center (registered at toetsingonline.nl, NL32117.018.10), all study procedures were performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

Reference cohort

We used normative data (ie, from adult members without a history of cancer) from the Dutch Lifelines cohort ($n = 132{,}226$, collected between 2007 and 2013) as a reference.[29] Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167 729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

Data collection

Demographic, disease- and therapy-related data, and information about recurrences and subsequent malignancies, had been extracted from medical records before recruitment (captured in the DCCSS-LATER database).[28] Therapy-related data included radiotherapy (RT) fields and fractionated dose, from which we calculated maximum body region dose. Additionally, we collected information on chemotherapy regimens and total cumulative doses, from which we estimated cyclophosphamide, steroid, and doxorubicin equivalent doses (Table S1). We selected thresholds for chemotherapy and RT doses based on clinical relevance and previous reports. Whether a participant had ever been diagnosed with growth hormone deficiency and/or hypogonadism was noted from medical charts.

Additional data were collected upon recruitment, along with a single late-effects outpatient clinic visit between June 2016 and February 2020.[27] Blood samples for serum lipid levels were intended to be drawn after overnight fasting and stored at −80 °C in a central biobank. Survivors underwent a physical examination for anthropometrics and completed various questionnaires, including a general health questionnaire (ie, history of disease, medication use, and lifestyle factors) and SQUASH (Short QUestionnaire to ASsess Health-enhancing physical activity).[30] We classified participants to have certain endocrine disorders (diabetes mellitus,

Table 1. Overview of earlier studies on dyslipidemia in CCSs.

Reference	Country	Definition of dyslipidemia	CCS (*N*=)	Age	Follow-up	Dyslipidemia (%)	Risk (versus controls)	Significant determinants
Goldberg et al.[8]	US (*SJLIFE*)	TG >150 mg/dL LDL-c > 160 mg/dL HDL-c < 40/50[a]mg/dL Non-HDL-c > 190 mg/dL	3406	M 35.2 y (10.4 SD)	M 26.7 y (10.6 SD)	TG: 17.2% LDL-c: 4.4% HDL-c: 30.1% Non-HDL-c: 5.8%	18.3%, $P = .53$ 4.0%, $P = .75$ 23.7%, $P = .01$ 23.7%, $P = .03$ (*Community controls*)	CRT, TBI for HSCT, age, race, hypertension, DM, CKD, positive family history, obesity, smoking, sedentary lifestyle
Agarwal et al.[9]	India	TG >150 mg/dL HDL-c < 40/50[a]mg/dL (*within METS-classification*)	500	Mdn 17 y (IQR 12-22)	Mdn 6 y (IQR 4-9)	TG: 9.6% HDL-c: 59.4%	NR	NR
Kepak et al.[10]	Czech Republic	Medical records	133	M 27.9 y (18-53)	M 16.8 y (5-43)	50%	NR	NR
Lipshultz et al.[11]	US (*COG*)	TC ≥200 mg/dL TG ≥150 mg/dL HDL-c < 40 mg/dL	164	Mdn 28.3y (16-38)	Mdn 17.5 (13-22)	TC: 28.8% TG: 18.8% HDL-c: 23.8% Known dyslipidemia: 3.7%	27.8%, $P = .82$ 17.4%, $P = .72$ 35.6%, $P = .004$ 3.3%, $P = .78$ *Controls = NHANES*	NR
Chow et al.[12]	US + Canada (*CCSS*)	Fasting TG ≥150 mg/dL (if <10 h fasting ≥200 mg/dL) LDL-c ≥ 160 mg/dL	571	Mdn 37.7 y (20.1-65.0)	Mdn 28.5 y (18.3-49.0)	History of dyslipidemia: 33.5% Medication use: 14.0% *% for measured abnormal lipid levels not reported*	21.7%, $P < .001$ 4.9%, $P < .001$ *Controls = NHANES*	NR
Schindera et al.[13]	Switzerland (*SURfit*)	TG ≥150 mg/dL or treatment HDL-c < 40/50[a] mg/dL or treatment (*within METS-classification*)	163	Mdn 28.4 y (IQR 23.4-36.6)	Mdn 22.3 y (IQR 16.0-29.1)	TG: 19% HDL-c: 18%	NR	NR
Nirmal et al.[14]	South India	TG ≥150 mg/dL HDL-c < 40/50[a]mg/dL (*within METS classification*)	277 (ALL)	Mdn 12.6 (6-29)	M 5.4 y (2.1-18.5)	TG: 24.9% HDL-c: 28.9%	NR	TG: overweight HDL-c: CRT, overweight
Chen et al.[15]	US + Canada (*CCSS*)	Self-reported prescription lipid-lowering agents use	22 643	Age 20, 25, 30, and 35 y	NR	20 y: 0.7% 25 y: 1.3% 30 y: 2.2% 35 y: 4.9%	NR	NR
Wilson et al.[16]	US (*SJLIFE*)	Fasting TC ≥200 mg/dL or TG ≥150 mg/dL or LDL-c ≥ 130 mg/dL or HDL-c < 40/50[a]mg/dL or treatment	431 (abd. tumor)	Mdn 29.9 y (18.7-55.1)	NR	Dyslipidemia: 47.2%-61.8% [b] TG: 18.4% HDL-c: 28.9% LDL-c: 18.9%	10.0%, $P < 0.001$ 33.5%, $P = .046$ 23.8%, $P = .26$	NR
Faber et al.[17]	Germany (*CVSS*)	Physician's diagnosis (CAPI, medical records) or fasting TG ≥ 150 mg/dL or LDL/HDL ratio > 3.5	951	M 34.0 y (23-48)	M 28.4 y (23-36)	28.3%	RR 1.26 (95% CI 1.12-1.42) (*Population-based controls, GHS*)	NR
Chao et al.[18]	US	Diagnosis in health registry (KPSC)	652	NR	M 6.2 y (0.04-16.0)	1.8%	IRR 1.9 (*Matched non-cancer comparison*)	NR

(*continued*)

Table 1. Continued

Reference	Country	Definition of dyslipidemia	CCS (*N*=)	Age	Follow-up	Dyslipidemia (%)	Risk (versus controls)	Significant determinants
Kero et al.[19]	Finland	Purchasing lipid-lowering drugs (DPR)	2530	Mdn 19.2 y (0-37.0)	Mdn 10.4 y (0-18.0)	NR	HR 4.3 (95%CI 0.9-19.5) (*sibling controls*)	ALL
Felicetti et al.[20]	Italy (*STROBE*)	TC = Fasting TC >200 mg/dL or LDL-c > 160 mg/dL TG = Fasting TG >200 mg/dL	340	M 24.1y (3.2 SD)	Mdn 16.1 y (5.1-33.0)	TC: 20% TG: 6%	NR	TC: TBI, GHD, auto-SCT, platinum-based therapy, older age at diagnosis TG: TBI, GHD
Nottage et al.[21]	US (*SJLIFE*)	TG ≥150 mg/dL or treatment LDL-c ≥ 130 mg/dL or treatment HDL-c < 40/50[a]mg/dL or treatment	784 (ALL)	Mdn 31.7 (18.9-59.1)	Mdn 26.1 y (11-45.3)	TG: 28.2% LDL-c: 31.8% HDL-c: 44.6%	OR 1.16 (NS) OR 1.14 (NS) OR 1.54 (significant) (*NHANES controls, adjusted for BMI*)	TG: CRT, male sex, white race LDL-c: CRT, older age HDL-c: CRT
Smith et al.[22]	US (*SJLIFE*)	TG ≥150 mg/dL HDL-c < 40/50[a]mg/dL (*within METS-classification*)	1598	Mdn 32.7 y (18.9-60.0)	M 25.6 y (7.6 SD)	TG: 33.8/21.0[a]% HDL-c: 38.2/ 42.6[a]%	NR	NR
Armstrong et al.[4]	US + Canada (*CCSS*)	Self-reported dyslipidemia diagnosis + lipid lowering agents use	10 724	Mdn 33.7 y (11-58.9)	Mdn 25.6 y (7.4-39.3)	At age 50 y: 23.0%	13.6%, *P* = .008 (*sibling controls*)	NR
Brouwer et al.[23]	NL	Fasting LDL-c ≥ 131.5 mg/dL and/ or use of lipid-lowering medication	277[c]	Mdn 27.5 (18.1-48.2)	Mdn 18.2 y (5.4-30.8)	33% Lipid lowering agents use: 1%	27%, *P* = .253 0% (*sibling controls*)	NR
Hudson et al.[24]	US (*SJLIFE*)	Fasting TC >200 mg/dL or TG ≥150 mg/dL or LDL ≥130 mg/ dL or HDL <40 mg/dL	1713	Mdn 32 y (18-60)	Mdn 25 y (10-47)	50.9%	Attributable fraction 15.5% (95% CI 10.2-20.5)	NR
Staba Hogan et al.[25]	US	Elevated TC and/or TG according CTCAE V3.0	168	Mdn 18.1 y (3-47.6)	Mdn 9.8 y (2.7-31.7)	16%	NR	NR
Meacham et al.[26]	US + Canada (*CCSS*)	Self-reported lipid lowering agents use	8599	M 32 y	NR	5.2%	4.0%, OR 1.6 (95% CI 1.3-2.0) (*sibling controls*)	Older age, TBI, Abd RT, chest RT, CRT

To identify studies that investigated the prevalence of dyslipidemia in CCS, we searched Pubmed in December 2023 by using the following search terms (including synonyms and words closely related): "dyslipidemia" or "hypercholesterolemia" or "hypertriglyceridemia" or "triglycerides" or "HDL" or "LDL" or "cholesterol" AND "cancer survivors" OR "childhood cancer survivor" or "history of cancer." We included papers in this table that (1) described CCS, (2) reported the prevalence of dyslipidemia and/or prevalence of abnormal lipid marker levels, (3) were written in English or Dutch language, and (4) were available in full text. We excluded studies that had (1) < 100 CCS in their cohort, (2) reported no prevalence of dyslipidemia and/or abnormal lipid level, and (3) reported no definition of dyslipidemia. We have converted all cutoffs reported to mg/dL to make the studies better comparable. Age and follow-up time reported as Median (Mdn) (range) or Mean (M) (range).

[a]Men/women.

[b]Dyslipidemia reported stratified per underlying diagnosis: bone tumor 61.8%; germ cell tumor 52.4%; neuroblastoma 60.0%; soft tissue sarcoma 45%; Wilms tumor 51.1%; other 47.2%

[c]Potentially cardiovascular toxic anticancer treatment (ie, anthracyclines, platinum, and/or RT)

Abbreviations: CCS, childhood cancer survivor; N, number; US, United States; SJLIFE, St. Jude Lifetime Cohort Study; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; M, mean; y, year; SD, standard deviation; CRT, cranial radiotherapy; TBI, total body irradiation; HSCT, hematopoietic stem cell transplantation; DM, diabetes mellitus; CKD, chronic kidney disease; METS, metabolic syndrome; Mdn, median; IQR, interquartile range; NR, not reported; COG, Children's Oncology Group; NHANES, National Health and Nutrition Examination Survey; CCSS, Childhood Cancer Survivor Study; ALL, acute lymphoblastic leukemia; abd, abdominal; CVSS, The cardiac and vascular late sequelae in long-term survivors of childhood cancer; CAPI, Computer-assisted personal interview; RR, relative risk; CI, confidence interval; GHS, Gutenberg Health Study; KPSC, Kaiser Permanente Southern California; IRR, Incidence Rate Ratio; DPR, Drug Purchase Registry; HR, hazard ratio; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology; GHD, growth hormone deficiency; NS, not significant; BMI, body mass index; CTCAE, common terminology criteria for adverse events.

dyslipidemia, hypothyroidism, hyperthyroidism, and renal failure) based on a combination of self-reported data and lab values. An overview of assessed covariates and their definitions, used laboratory assays, cutoff values, and references are depicted in Table S1.

For the reference cohort, demographics, anthropometrics, laboratory results (lipid levels), and questionnaire derived information (medical history, medication use, and lifestyle factors) were provided by Lifelines.[29]

Dyslipidemia

In the current study, we employed three methods to classify dyslipidemia, which was based on a single lipid profile obtained during the outpatient clinic visit combined with self-reported data on lipid-lowering agents use (ACT code C10) (Table 2). First, we looked at specific lipid abnormalities, including triglycerides >1.7 mmol/L, HDL-c < 1.0/1.3 mmol/L (men/women), LDL-c > 4.1 mmol/L, total cholesterol >5.2 mmol/L, and apolipoprotein-B > 130 mg/dL, and/or treatment. Second, we analyzed our data utilizing the embedded dyslipidemia definitions within metabolic syndrome classifications (NCEP-ATP-III, JIS, WHO, and EGIR), which rely on thresholds for triglycerides and HDL-c in combination with lipid-lowering agents use (Table 2). Third, we used the CTCAE v4.03 criteria (grade ≥1 and ≥2) for dyslipidemia, which relies on thresholds for triglycerides and total cholesterol in combination with lipid-lowering agents use (Table 2). As lipid values are influenced by the use lipid-lowering agents, we also explored dyslipidemia according above methods in a cohort of participants without prior lipid-lowering agents use.

Statistical analysis

Demographic, disease- and therapy-related characteristics were reported by using descriptive statistics. Comparisons between the survivor and reference cohort were assessed using χ^2 or Fisher's exact test as appropriate. To investigate the association between the prevalence of dyslipidemia and different cohorts (ie, survivor and reference cohort), multivariable logistic regression models, adjusted for age, sex, and BMI, were estimated. Odds ratios (OR) and 95% confidence intervals are provided. Potential determinants associated with dyslipidemia (according to specific lipid abnormalities, CTCAE v4.03 (grade ≥1), and NCEP-ATP-III) were identified by estimating univariable logistic regression models. Demographic (age, sex, follow-up time), lifestyle (body mass index (BMI), smoking, heavy drinking, and low physical activity), and treatment factors (major groups of RT and chemotherapeutics, and hematopoietic stem cell transplantation (HSCT)) were considered as potential risk factors. Significant variables ($P < .05$) in univariable analysis and patient factors known to be relevant from literature (age, sex, and follow-up time) were included in the multivariable models. Treatment variables were incorporated as categorized variables when possible. To avoid mediation by endocrine deficiencies caused by treatment factors, we estimated separate multivariable models for (1) treatment-related risk factors and (2) endocrine comorbidity-related risk factors. The interaction term between sex and age was incorporated in the models. We investigated the presence of multicollinearity by calculating variance inflation factors. P-values below .05 were considered as significant. All analyses were conducted in R (version 4.0.3; Vienna, Austria).[31]

Results

Of the 4671 invited survivors, 2338 (50.1%) participated in the current study (Figure S1). In our survivor cohort (51.2% male), the median age at recruitment was 34.7 years (range 18.2-70.8) and median follow-up time was 27.1 years (range 14.8-54.7). The baseline and sex-stratified characteristics are depicted in Table 3 and Table S2, respectively. We obtained a complete lipid profile from 2219 (94.9%) participants and information on lipid-lowering agents was available in 2117 (90.5%) participants. In total, 2007 survivors (85.8%) did report no prior lipid-lowering agents use (Table S3), compared to 126 631 (95.8%) participants in the reference cohort. Comparing participants to non-participants, participants were more likely to be female, to be exposed to RT as well as chemotherapy and to a prior HSCT. We observed no differences regarding age at diagnosis and recruitment, and follow-up time (Table S4).

Prevalence and odds of dyslipidemia

In the survivor cohort, 5.2% participants reported to use lipid-lowering agents, compared to 4.1% in the reference cohort ($P = .016$), even though the survivor cohort was significantly younger compared to the reference cohort (median 34.7 vs 43.0 years, respectively). The adjusted OR for treatment in survivors was 2.88 (95% CI = 2.33-3.57). The prevalence of dyslipidemia in the survivor cohort, defined by specific lipid abnormalities and/or treatment with lipid-lowering agents, was 25.7%, 34.2%, 34.6%, 12.6%, and 13.0% for high triglycerides, low HDL-c, high total cholesterol, high LDL-c, and high Apolipoprotein-B, respectively. In the reference cohort, this was 17.6%, 18.0%, 41.3%, 18.4%, and 21.3%, respectively (all $P < .001$) (Table 4 and Figure 1). When comparing the prevalence of dyslipidemia according to the different classifications, we identified a variation in prevalence between 29.0% and 45.3% in the survivor cohort and 15.6%-45.5% in the reference cohort. All classifications translated into a significantly higher prevalence of dyslipidemia in survivors versus references, in both males and females and in all age groups (Figure 2). Men showed an increasing trend in prevalence of dyslipidemia with increasing age for all classifications ($P < .001$ in a logistic regression model analyzing dyslipidemia (NCEP-ATP-III) as a function of age). Women seemed to show a more constant prevalence of dyslipidemia ($P = .218$ in the logistic regression model analyzing dyslipidemia (NCEP-ATP-III) as a function of age) (Figure 2). All classifications also translated into significantly higher odds of dyslipidemia in survivors compared to the references, adjusted for age, sex, and BMI, with corresponding ORs between 1.55 (95% CI = 1.41-1.71) and 2.95 (95% CI = 2.65-3.28) for CTCAE v4.03, grade ≥1 and EGIR, respectively (Table 4). According the NCEP-ATP-III criteria, survivors with underlying CNS tumors had a significantly higher prevalence of dyslipidemia (48.5%) compared to those with underlying hematologic malignancies or solid tumors (38.0% and 38.6%, respectively). The prevalence of the serum lipid abnormalities did not significantly differ between survivors with underlying hematologic malignancies, solid tumors or CNS tumors (Tables S5 and S6).

Prevalence and odds of dyslipidemia in participants without lipid-lowering agents

In survivors without lipid-lowering agents, the prevalence of specific lipid abnormalities was 20.6%, 30.3%, 29.9%,

Table 2. Used definitions and classifications of dyslipidemia.

	Specific lipid abnormalities	NCEP-ATP-III[a]/JIS[b]	WHO[c]	EGIR[d]	CTCAE v4.03[e] Grade 1 or higher	CTCAE v4.03[e] Grade 2 or higher
Triglycerides mmol/L (mg/dL)	>1.7 (>150) or treatment	≥1.7 (≥150) or treatment	≥1.7 (≥150) or treatment	>2.0 (>178) or treatment	>1.7 (>150) or treatment	>3.4 (>300) or treatment
HDL-c mmol/L (mg/dL)	<1.0 (<40)[f] < 1.3 (<50)[g] or treatment	<1.0 (<40)[f] < 1.3 (<50)[g] or treatment	<0.9[f] (<35)[f] < 1.0[g] (<39)[g] or treatment	<1.0 (<39) or treatment		
Total cholesterol mmol/L (mg/dL)	>5.2 (>200) or treatment				>5.2 (>200) or treatment	>7.8 (>300) or treatment
LDL-c mmol/L (mg/dL)	>4.1 (>160) or treatment					
Apolipoprotein-B mg/dL	>130[h] or treatment					

This table shows the different criteria of dyslipidemia used in the current study and their corresponding cutoff values. The presence of only one factor (ie, lipid abnormality or treatment with drugs under ATC code C10, ie, lipid lowering agents) per classification is sufficient for the diagnosis of dyslipidemia. The classifications by the NCEP-ATP-III, JIS, WHO, and EGIR for dyslipidemia are embedded in a broader definition for metabolic syndrome.

Abbreviations: HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; JIS, Joint Interim Statement of International Diabetes Federation; National Heart, Lung, and Blood Institute; and the American Heart Association; WHO, World Health Organization; EGIR, European Group for the Study of Insulin Resistance; CTCAE, NCI Common Terminology Criteria for Adverse Events, v4.03 being the modified version.

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[f]Men.

[g]Women.

[h]Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019; 139(25): e1082-e143.

Table 3. Baseline characteristics of survivor and reference cohort.

	Survivor cohort N = 2 338[a]	Reference cohort N = 132 226[a]	Comparison (P-value)
Sex			
Male	1198 (51.2)	54 763 (41.4)	
Female	1140 (48.8)	77 463 (58.6)	
Age at outpatient clinic visit (years)			
18-30	728/2326 (31.3)	20 819 (15.7)	**<.001**
30-39	883/2326 (38.0)	30 042 (22.7)	**<.001**
40-49	550/2326 (23.6)	49 040 (37.1)	**<.001**
>50	165/2326 (7.1)	32 325 (24.4)	**<.001**
BMI[b]			
>25 kg/m^2	1025/2252 (45.5)	69 989/132 150 (53.0)	**<.001**
>30 kg/m^2	306/2252 (13.6)	19 941/132 150 (15.1)	**.048**
>35 kg/m^2	87/2252 (3.9)	4966/132 150 (3.8)	.794
Lifestyle characteristics			
Smoking	665/2048 (32.5)	28 437/127 358 (22.3)	**<.001**
Heavy drinking	59/902 (6.5)	NA	
Low physical activity	436/1709 (25.5)	56 955/117 803 (48.3)	**<.001**
Age at diagnosis (years)			
0-4	1071 (45.8)	–	
5-9	651 (27.8)	–	
10-14	481 (20.6)	–	
15-17	135 (5.8)	–	
Primary childhood cancer			
Hematologic malignancies	1279 (54.7)	–	
Solid tumors	843 (36.1)	–	
CNS neoplasms	213 (9.1)	–	
Other and unspecified neoplasms	3 (0.1)	–	
Follow-up time since diagnosis (years)			
10-20	472 (20.2)	–	
20-30	928 (39.7)	–	
30-40	693 (29.6)	–	
40-50	220 (9.4)	–	
50-59	25 (1.1)	–	
Surgery[c]			
Yes	1145/2331 (49.1)	–	
Amputation	67 (2.9)	–	
RT[c]			
Any RT	905/2337 (38.7)	–	
Abdominal/pelvic	201/2327 (8.6)	–	
Cranial[d]	432/2330 (18.5)	–	
Total body	88/2327 (3.8)	–	
Chemotherapy[c]			
Any chemotherapy	2057 (88.0)	–	
Alkylating agents	1176/2126 (55.3)	–	
Anthracyclines	1172/2204 (53.2)	–	
Asparaginase	584/2335 (25.0)	–	
Corticosteroids	1190/2338 (50.9)	–	
Platinum	311/2335 (13.3)	–	
Vinca alkaloids	1829/2336 (78.3)	–	
Bone marrow transplant[c]			
With myeloablative conditioning	137/2322 (5.9)	–	
Therapy[c]			
No treatment	10/2337 (0.4)	–	
Surgery only	150/2337 (6.4)	–	
Chemotherapy only (± surgery)	1272/2337 (54.4)	–	
RT only (± surgery)	121/2337 (5.2)	–	
Chemotherapy and RT (± surgery)	784/2337 (33.5)	–	

P-values for comparison were obtained using Pearson's χ^2 test. Significant values ($P < 0.05$) are displayed in bold.
Abbreviations: BMI, Body Mass Index; CNS, central nervous system; N, number.
[a]Not all numbers and percentages add up to group total because of variating missing data per subgroup. In groups with missing values, the total number of participants with an outcome for this variable is included in the table (after the slash).
[b]Weight is adjusted for amputated limbs by adding percentage to body weight (based on given amputation).
[c]Primary cancer and recurrences.
[d]Including cranial irradiation (brain tumors) and craniospinal irradiation.

7.3%, and 7.7% for high triglycerides, low HDL-c, high total cholesterol, high LDL-c, and high apolipoprotein-B, respectively. This was 13.9% ($P < .001$), 14.3% ($P < .001$), 38.7% ($P < .001$), 14.7% ($P < .001$), and 6.3% ($P = .02$) in the corresponding reference cohort (Table 5). In both the survivor and the reference cohort, all lipid abnormalities, except for low HDL-c levels, had an increasing trend in prevalence with increasing age (Figure 1 and Figure S2). Similar results

Table 4. Prevalence of dyslipidemia, including OR and 95% confidence interval, in all participants.

	Survivor cohort N = 2 338[a]	Reference cohort N = 132 226[a]	OR (95% CI)	Adjusted OR (95% CI)[b]
Lipid abnormalities				
High triglycerides (>1.7 mmol/L) or treatment	573/2231 (25.7)	22 543/128 119 (17.6)	**1.62 (1.47-1.78)**	**2.20 (1.98-2.44)**
Low HDL-c (<1.0/<1.3[c] mmol/L) or treatment	762/2230 (34.2)	23 076/128 118 (18.0)	**2.36 (2.16-2.58)**	**2.81 (2.55-3.08)**
High total cholesterol (>5.2 mmol/L) or treatment	773/2231 (34.6)	52 972/128 119 (41.3)	**0.75 (0.69-0.82)**	**1.23 (1.12-1.35)**
High LDL-c (>4.1 mmol/L) or treatment	280/2230 (12.6)	23 561/128 110 (18.4)	**0.64 (0.56-0.72)**	1.01 (0.89-1.16)
High apolipoprotein-B (>130 mg/dL) or treatment	289/2231 (13.0)	7300/34 193 (21.3)	**0.55 (0.48-0.62)**	**1.20 (1.04-1.38)**
Classifications				
NCEP-ATP III/JIS	963/2127 (45.3)	34 475/128 036 (26.9)	**2.25 (2.06-2.45)**	**2.64 (2.41-2.90)**
WHO	650/2103 (30.9)	24 358/128 026 (19.0)	**1.90 (1.73-2.09)**	**2.52 (2.27-2.79)**
EGIR	605/2089 (29.0)	19 981/128 023 (15.6)	**2.20 (2.00-2.43)**	**2.95 (2.65-3.28)**
CTCAE v4.03, grade ≥1	959/2135 (44.9)	58 274/128 073 (45.5)	0.98 (0.90-1.06)	**1.55 (1.41-1.71)**
CTCAE v4.03, grade ≥2	190/2039 (9.3)	8187/128 009 (6.4)	**1.50 (1.29-1.75)**	**2.73 (2.31-3.21)**
Treatment				
Self-reported lipid lowering agents use	110/2117 (5.2)	5477/132 108 (4.1)	**1.27 (1.04-1.54)**	**2.88 (2.33-3.57)**

Significant values ($P < 0.05$) are displayed in bold. Abbreviations: HDL-c, High density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; NCEP-ATP-III, National Cholesterol Education Program Adult Treatment Panel III; JIS, Joint Interim Statement of International Diabetes Federation; National Heart, Lung, and Blood Institute; and the American Heart Association; WHO, World Health Organization; EGIR, European Group for the Study of Insulin Resistance; CTCAE v4.03, Modified version of the NCI Common Terminology Criteria for Adverse Events; N, number; CI, confidence interval.
[a]Number of participants per outcome varies due to alternating missing values. Total number of participants per cohort is mentioned in upper row. For all groups with missing values, the total number of participants with an outcome for this variable is included behind the slash.
[b]Adjusted for age, sex, and BMI.
[c]Men/Women.

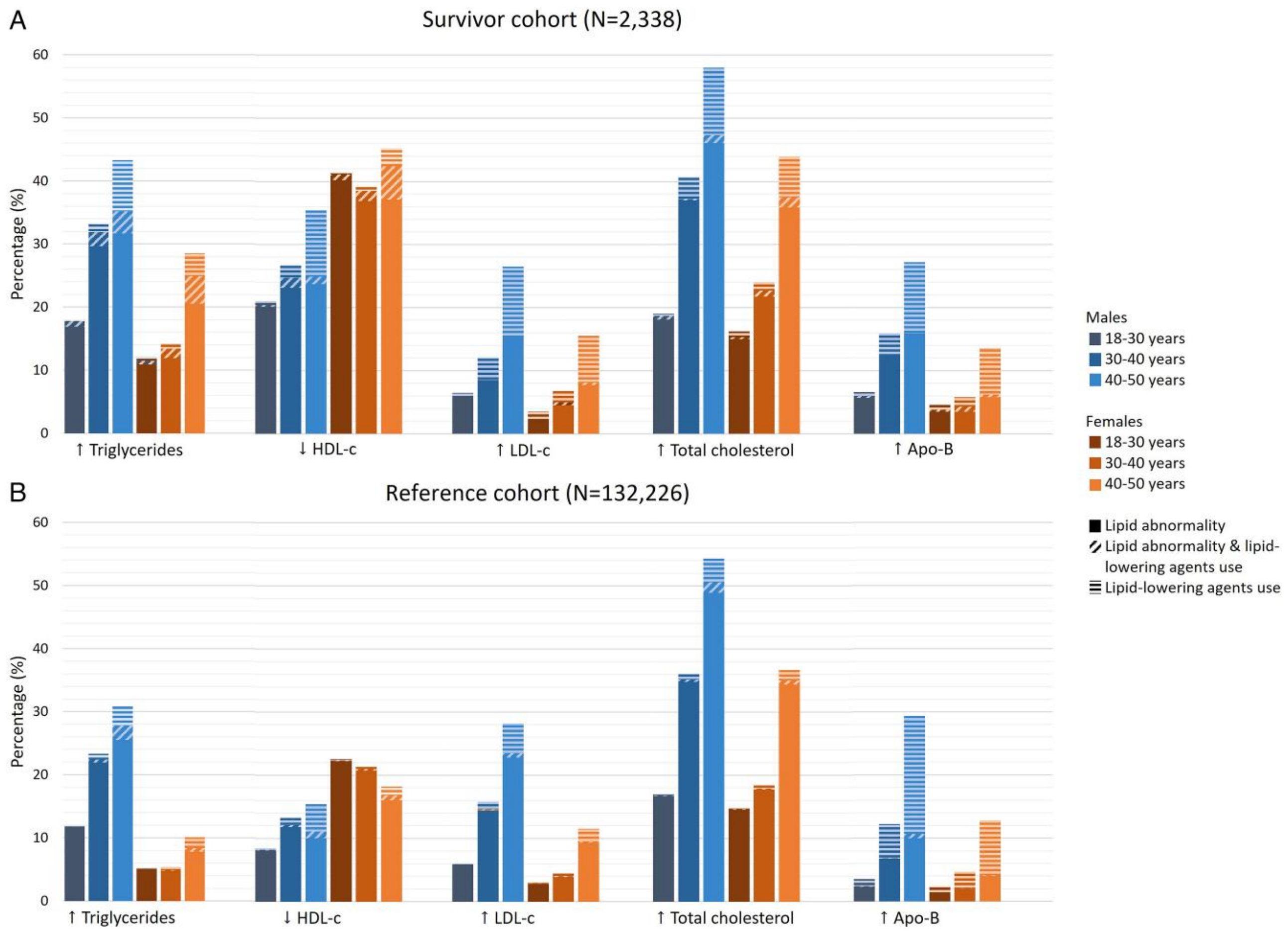

Figure 1. Due to the small number of participants >50 years in our survivor cohort, with also a skewed distribution within the age-group compared to the reference cohort, this age-group was not included in the figure. Abnormal triglyceride and HDL-c were significantly more prevalent in the survivor cohort compared to the reference cohort in all age-groups (both males and females). Abnormal LDL-c was only significantly different between the survivor and reference cohort for males aged 30-40 years and abnormal total cholesterol only for females aged 30-40 and 40-50 years. Abnormal Apo-B was significantly more prevalent in the survivor cohort for males aged 18-30 and 30-40 years, and for females 18-30 years. The prevalence of lipid abnormalities excluding participants with lipid-lowering agents is shown in Figure S2. Abbreviations: HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Apo-B, apolipoprotein-B.

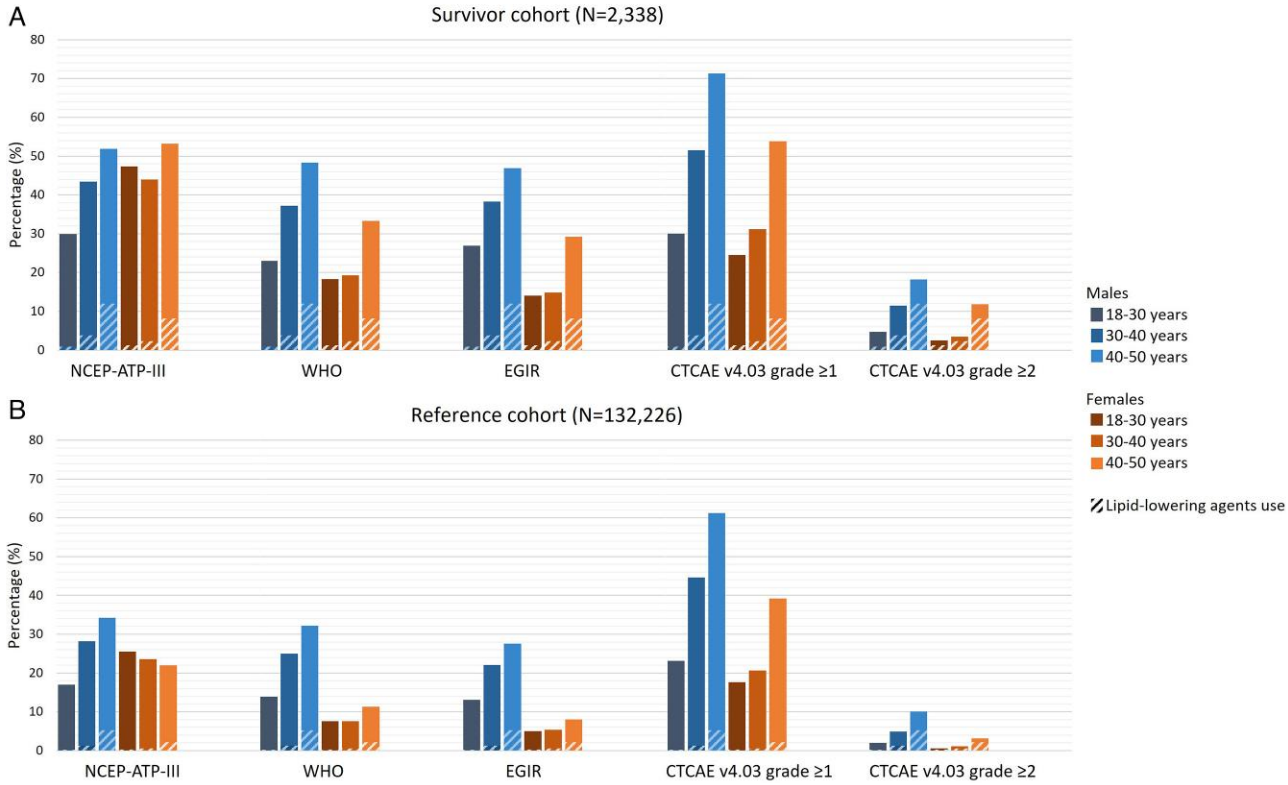

Figure 2. Due to the small number of participants >50 years in our survivor cohort, with also a skewed distribution within the age-group compared to the reference cohort, this age-group was not included in the figure. Survivors, both males and females, had a significantly higher prevalence of dyslipidemia according all classifications in all age-groups. Abbreviations: NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; WHO, World Health Organization; EGIR, European Group for the Study of Insulin Resistance; CTCAE, NCI Common Terminology Criteria for Adverse Events, v4.03 being the modified version.

Table 5. Prevalence of dyslipidemia, including OR and 95% confidence interval, in participants without lipid-lowering agents.

	Survivor cohort N = 2 007[a]	Reference cohort N = 126 631[a]	OR (95% CI)	Adjusted OR (95% CI)[b]
Lipid abnormalities				
High triglycerides (>1.7 mmol/L) or treatment	395/1914 (20.6)	17 046/122 528 (13.9)	**1.61 (1.44-1.80)**	**1.89 (1.68-2.13)**
Low HDL-c (<1.0/<1.3[c] mmol/L) or treatment	580/1913 (30.3)	17 582/122 527 (14.3)	**2.60 (2.35-2.87)**	**2.73 (2.46-3.03)**
High total cholesterol (>5.2 mmol/L) or treatment	573/1914 (29.9)	47 435/122 528 (38.7)	**0.68 (0.61-0.75)**	1.08 (0.97-1.20)
High LDL-c (>4.1 mmol/L) or treatment	139/1913 (7.3)	18 054/122 519 (14.7)	**0.45 (0.38-0.54)**	**0.69 (0.58-0.82)**
High apolipoprotein-B (>130 mg/dL) or treatment	147/1914 (7.7)	1821/28 688 (6.3)	**1.23 (1.03-1.46)**	**1.84 (1.53-2.20)**
Classifications				
NCEP-ATP III/JIS	750/1914 (39.2)	28 966/122 527 (23.6)	**2.08 (1.90-2.28)**	**2.23 (2.02-2.46)**
WHO	461/1914 (24.1)	18 859/122 527 (15.4)	**1.74 (1.57-1.94)**	**2.00 (1.78-2.24)**
EGIR	430/1914 (22.5)	14 485/122 527 (11.8)	**2.16 (1.94-2.41)**	**2.39 (2.12-2.69)**
CTCAE v4.03, grade ≥1	738/1914 (38.6)	52 729/122 528 (43.0)	**0.83 (0.76-0.91)**	**1.29 (1.17-1.43)**
CTCAE v4.03, grade ≥2	65/1914 (3.4)	2706/122 528 (2.2)	**1.56 (1.21-2.00)**	**1.86 (1.44-2.41)**
Treatment				
Self-reported lipid lowering agents use	0 (0.0)	0 (0.0)	NA	NA

Significant values ($P < 0.05$) are displayed in bold. Abbreviations: HDL-c, high density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NCEP-ATP-III, National Cholesterol Education Program Adult Treatment Panel III; JIS, Joint Interim Statement of International Diabetes Federation; National Heart, Lung, and Blood Institute; and the American Heart Association; WHO, World Health Organization; EGIR, European Group for the Study of Insulin Resistance; CTCAE v4.03, Modified version of the NCI Common Terminology Criteria for Adverse Events; N, number; CI, confidence interval.
[a]Number of participants per outcome varies due to alternating missing values. Total number of participants per cohort is mentioned in upper row. For all groups with missing values, the total number of participants with an outcome for this variable is included behind the slash.
[b]Adjusted for age, sex, and BMI.
[c]Men/women.

were observed when comparing the mean lipid biomarker values per year of age subsets in our survivor and reference cohort (Figure 3 and Figure S3). Survivors without lipid-lowering agents had increased odds of high triglycerides (aOR = 1.89, 95% CI = 1.68-2.13), low HDL-c (aOR = 2.73, 95% CI = 2.46-3.03), and high Apolipoprotein-B (aOR = 1.84, 95% CI = 1.53-2.20) levels compared to the corresponding reference cohort. The odds for high total cholesterol levels were not significantly different between both cohorts and for high LDL-c levels, decreased odds for the survivors without lipid-lowering agents

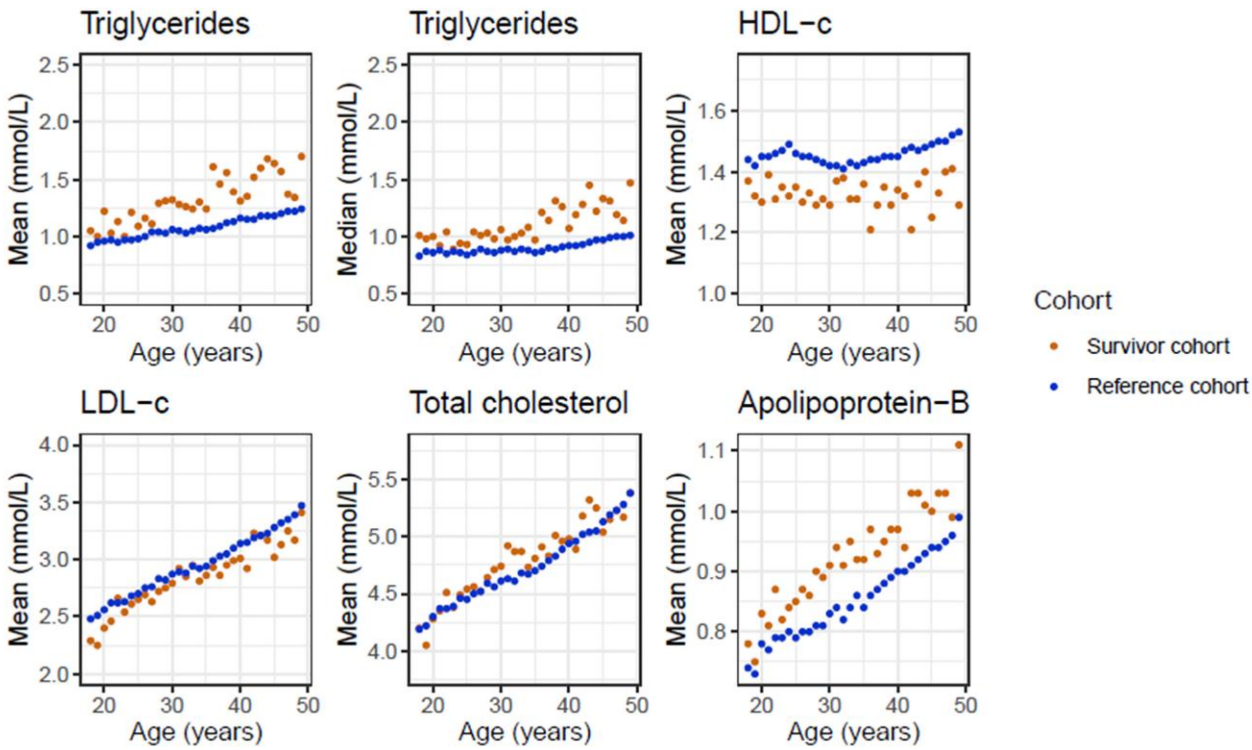

Figure 3. Visualization of the mean/median levels of separate lipids per year of age in participants without lipid lowering agents (*n* = 2007 in survivor and *n* = 126,631 in reference cohort). Due to triglycerides being not normally distributed, we show the median next to the mean. All other lipid biomarkers were normally distributed in both cohorts. Sex-stratified figures are depicted in Figure S3a and b. Abbreviations: HDL-c, High density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol.

compared to corresponding references were found (aOR = 0.69, 95% CI = 0.58-0.82) (Table 5).

Underdiagnoses

Among the participants with lipid abnormalities during study measurements, between 81.4% (high Apo-B levels) and 88.9% (high total cholesterol levels) had no prior diagnosis of dyslipidemia (self-report). As for the different classifications of dyslipidemia, this percentage of underdiagnosed participants differed between 71.1% (CTCAE v4.03, grade ≥2) and 87.7% (NCEP-ATP-III) (Table S7).

Determinants of dyslipidemia

Univariable logistic regression analysis identified numerous determinants associated with specific lipid abnormalities as well as with dyslipidemia defined by NCEP-ATP-III and CTCAE v4.03 (grade ≥1) in CCS (Tables S5 and S6). Multivariable logistic regression analysis identified sex, age, the interaction between sex and age, BMI, physical activity, smoking, abdominal RT, cranial RT, TBI, alkylating agents, diabetes mellitus, and growth hormone deficiency to be significantly associated with at least one of the abnormal lipid values in survivors without lipid-lowering agents (Tables 6 and 7). In the multivariable model with dyslipidemia according the NCEP-ATP-III criteria as an outcome, the interaction effect between age and sex was significant, indicating that the degree of association between each predictor and the outcome changes according to the levels of the other predictor: $OR_{sex} = 3.03$, 95% CI = 2.06-4.49, if age group 18-30 year; $OR_{sex} = 1.02$, 95% CI = 0.72-1.44, if age group 30-40 year; $OR_{sex} = 1.16$, 95% CI = 0.71-1.90, if age group >40 year (Table 8). Additionally, BMI at time of recruitment (OR = 1.16, 95% CI = 1.13-1.20 per BMI point) was significantly associated with the outcome. Treatment variables, including prior abdominal/pelvic RT (OR = 2.41, 95% CI = 1.28-4.60 for >30 Gy), cranial RT (OR = 2.07, 95% CI = 1.30-3.32 for 1-25 Gy), total body irradiation (OR = 7.81, 95% CI = 4.13-15.35) and administered cyclophosphamide equivalent dose (OR = 1.44, 95% CI = 1.01-2.05 and OR = 1.97, 95% CI = 1.43-2.72 for 4000-8000 and >8000 g/m^2, respectively) were significantly associated as well (Table 8). In a separate model for endocrine comorbidity-related determinants, we also identified diabetes mellitus (OR = 4.32, 95% CI = 2.18-9.22), growth hormone deficiency (OR = 1.74, 95% CI = 1.05-2.90) and hyperthyroidism at time of recruitment (OR = 2.43, 95% CI = 1.10-5.66) to be associated with this outcome. Using the CTCAE v4.03 (grade ≥1) instead of NCEP-ATP-III criteria as an outcome, similar associations were found except for the variable physical activity. Physical activity was associated with dyslipidemia (CTCAE criteria, OR = 1.42, 95% CI = 1.08-1.88), but not when dyslipidemia was defined using the NCEP-ATP criteria (OR = 1.25, 95% CI = 0.96-1.62) (Table 8). Due to the high number of missing values of low physical activity (18.9% and 51.3% missing in participants aged <40 year and >40 year, respectively), we also show the estimated models excluding this determinant (Tables S8-S10).

Discussion

CVD is the leading cause of morbidity and mortality in CCSs.[2-4] Dyslipidemia is a well-recognized and modifiable risk factor for atherosclerotic cerebrovascular and CVD.[5,8]

Table 6. Treatment related determinants for specific lipid abnormalities using multivariable logistic regression analysis.

	Triglycerides >1.7 mmol/L OR (95% CI)	HDL-c < 1.0/ 1.3[a]mmol/L OR (95% CI)	LDL-c > 4.1 mmol/L OR (95% CI)	Total cholesterol >5.2 mmol/L OR (95% CI)	Apo-B > 130 mg/dL OR (95% CI)
Sex (female)	0.81 (0.48-1.37)	**3.67 (2.42-5.63)**	**0.34 (0.20-0.58)**	0.85 (0.52-1.37)	**0.22 (0.12-0.38)**
Age (outpatient clinic visit)					
18-29 y	REF	REF	REF	REF	REF
30-39 y	1.45 (0.90-2.37)	0.96 (0.61-1.52)	1.26 (0.63-2.59)	**2.29 (1.48-3.59)**	1.86 (0.97-3.67)
>40 y	1.31 (0.66-2.59)	0.63 (0.32-1.20)	2.14 (0.82-5.58)	**2.94 (1.61-5.39)**	2.47 (0.96-6.38)
Follow-up time (per year)	1.02 (0.98-1.05)	1.02 (0.99-1.04)	1.02 (0.96-1.07)	1.01 (0.98-1.04)	0.98 (0.93-1.03)
BMI (per point)	**1.12 (1.09-1.16)**	**1.16 (1.12-1.20)**	**1.07 (1.02-1.12)**	**1.04 (1.02-1.08)**	**1.11 (1.06-1.16)**
Low physical activity (yes vs no)	**1.64 (1.18-2.27)**	1.19 (0.89-1.58)	**1.72 (1.03-2.81)**	1.24 (0.93-1.66)	**1.68 (1.01-2.74)**
Smoking (yes vs no)	–	–	1.60 (0.99-2.58)	–	1.58 (0.98-2.53)
Treatment characteristics					
Abdominal/Pelvic RT (yes vs no)	–	–	1.30 (0.47-3.06)	–	1.98 (0.77-4.47)
Abdominal/Pelvic RT (Gy)					
0	REF	–	–	REF	–
1-30	0.86 (0.36-1.83)	–	–	1.03 (0.53-1.92)	–
>30	**2.48 (1.17-5.07)**	–	–	1.77 (0.89-3.45)	–
Cranial RT (yes vs no)	–	–	**2.23 (1.26-3.88)**	–	**2.21 (1.24-3.85)**
Cranial RT (Gy)					
0	REF	REF	–	REF	–
1-25	**2.11 (1.21-3.64)**	**1.92 (1.19-3.10)**		**1.98 (1.20-3.25)**	–
>25	1.42 (0.77-2.54)	1.38 (0.79-2.36)	–	1.67 (0.97-2.83)	–
TBI (yes vs no)	**10.30 (5.03-21.39)**	3.91 (2.03-7.47)	–	1.82 (0.90-3.57)	**2.88 (1.00-7.28)**
Alkylating agents (yes vs no)	–	–	**1.92 (1.16-3.27)**	–	1.47 (0.89-2.47)
Alkylating agents (mg/m^2)					
0	REF	REF	–	REF	–
1-4000	0.91 (0.58-1.40)	1.14 (0.82-1.59)	–	1.24 (0.85-1.81)	–
4000-8000	**1.90 (1.23-2.92)**	**1.50 (1.02-2.18)**	–	1.63 (1.11-2.37)	–
>8000	**1.83 (1.22-2.75)**	**1.87 (1.31-2.66)**	–	**1.03 (0.71-1.48)**	–
Asparaginase (yes vs no)[b]	–	–	–	0.80 (0.54-1.17)	–
Corticosteroid (mg/m^2)					
0	REF	–	–	REF	–
1-10,000	0.81 (0.56-1.16)	–	–	0.73 (0.52-1.03)	–
>10,000	0.62 (0.28-1.31)	–	–	0.93 (0.45-1.86)	–
Platinum (yes vs no)[c]	–	–	0.66 (0.28-1.37)	–	–
Interaction terms sex: age					
Female: age group 30-40 y	**0.34 (0.17-0.69)**	**0.50 (0.28-0.88)**	–	**0.53 (0.29-0.98)**	–
Female: age group >40 y	0.56 (0.25-1.26)	0.74 (0.37-1.51)	–	0.82 (0.41-1.64)	–

Significant values ($P < 0.05$) are displayed in bold.
In the current analysis, $n = 2007$ participants without lipid-lowering agents were included. Models were adjusted for all variables included in the model. Cells denoted by "–" indicate that we did not include this variable in the model. Due to the high number of missing values of the determinant low physical activity (18.9% and 51.3% missing in age groups <40 y and >40 y, respectively), the multivariable models without low physical activity are shown in Table S8.
Abbreviations: HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Apo-B, apolipoprotein-B; OR, odds ratio; 95%CI, 95% confidence interval; y, year; REF, reference; RT, radiotherapy; Gy, gray; TBI, total body irradiation.
[a]Men/women.
[b]Asparaginase agents included asparaginase, pegasparaginase, erwinase, paronal, and crasnitin.
[c]Platinum agents includes cisplatin and carboplatin.

We observed an increased odds of dyslipidemia in our survivor cohort compared to the general population. As dyslipidemia is a condition that is typically observed in the elderly population, the prevalence of dyslipidemia was relatively high in our young adult survivor population (median age 34.0 years), underscoring the previously described "accelerated aging" phenotype in CCS.[32] This information, combined with the already known existent risk factors for CVD in CCS,[4] illustrates the importance of regular lipid monitoring in CCS at an even younger age compared to what is recommended in the general population. This is even more relevant as we noticed that 70%-90% of our survivors with abnormal lipid levels during study measurements had not yet been identified as patients with dyslipidemia in routine clinical care.

Commonly used risk assessment tools that include lipid biomarker thresholds are often not designed for younger adults (Framingham score >30 years and SCORE2 > 40 years).[33,34] Premature aging and high-risk cancer treatment exposures are not considered in these models, which may result in an underestimation of CVD risk in CCS. The Children's Oncology Group reported lower predicted CVD risk in CCS compared to population matched controls when applying the Framingham score, but moderate or greater risk of future CVD predicted by a survivor-specific risk model.[11] Unfortunately, these survivor specific risk models for CVD, made by the Childhood Cancer Survivor Study (CCSS), do not include lipid biomarker thresholds.[15] Such risk assessment tools, designed specifically for young adult CCS and considering cardiovascular risk factors as well as cancer treatment exposures, could be enhanced by adding lipid level thresholds to not only reliably identify survivors at risk, but also provide accrued recommendations on which CCS would benefit from lipid lowering agents to avoid cardiovascular morbidity and mortality.

Table 7. Comorbidity related determinants for specific lipid abnormalities using multivariable logistic regression analysis.

	Triglycerides > 1.7 mmol/L OR (95% CI)	HDL-c < 1.0/ 1.3[a]mmol/L OR (95% CI)	LDL-c > 4.1 mmol/L OR (95% CI)	Total cholesterol >5.2 mmol/L OR (95% CI)	Apo-B > 130 mg/dL OR (95% CI)
Sex (female)	0.69 (0.41-1.13)	**3.39 (2.27-5.11)**	**0.39 (0.24-0.62)**	**0.59 (0.46-0.75)**	**0.25 (0.15-0.41)**
Age (outpatient clinic visit)					
18-29 y	REF	REF	REF	REF	REF
30-39 y	**1.83 (1.17-2.87)**	1.20 (0.78-1.85)	1.26 (0.66-2.46)	**1.95 (1.41-2.71)**	**2.12 (1.16-4.03)**
>40 y	1.57 (0.83-2.96)	0.85 (0.45-1.57)	**2.78 (1.14-6.79)**	**3.26 (2.00-5.32)**	**3.33 (1.38-8.10)**
Follow-up time (per year)	1.01 (0.99-1.04)	1.01 (0.98-1.03)	1.00 (0.96-1.05)	1.00 (0.98-1.03)	0.97 (0.92-1.01)
BMI (per point)	**1.10 (1.06-1.13)**	**1.14 (1.11-1.18)**	**1.08 (1.04-1.13)**	**1.04 (1.01-1.07)**	**1.10 (1.06-1.15)**
Low physical activity (yes vs no)	**1.65 (1.22-2.23)**	1.20 (0.91-1.57)	**1.68 (1.05-2.66)**	1.21 (0.92-1.58)	1.58 (0.98-2.49)
Smoking (yes vs no)	–	–	**1.59 (1.02-2.49)**	–	**1.62 (1.04-2.49)**
Comorbidities					
Diabetes Mellitus (yes vs no)	**4.44 (2.08-9.51)**	**2.39 (1.10-5.23)**	–	–	–
GHD (yes vs no)	1.21 (0.67-2.14)	**1.83 (1.10-3.02)**	**2.43 (1.13-4.96)**	**1.89 (1.16-3.04)**	**2.89 (1.45-5.48)**
Hypogonadism (yes vs no)	1.49 (0.79-2.72)	–	1.49 (0.60-3.40)	–	–
Interaction terms sex: age					
Female: age group 30-40 y	**0.35 (0.18-0.68)**	**0.45 (0.26-0.78)**	–	–	–
Female: age group >40 y	0.71 (0.33-1.51)	0.65 (0.33-1.27)	–	–	–

Significant values ($P < 0.05$) are displayed in bold.
In the current analysis, $n = 2007$ participants without lipid-lowering agents were included. Models were adjusted for all variables included in the model. Cells denoted by "–" indicate that we did not include this variable in the model. Due to the high number of missing values of the determinant low physical activity (18.9% and 51.3% missing in age groups <40 y and >40 y, respectively), the multivariable models without low physical activity are shown in Table S9.
Abbreviations: HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Apo-B, apolipoprotein-B; OR, odds ratio; 95%CI, 95% confidence interval; y, year; REF, reference; BMI, body mass index; GHD, growth hormone deficiency.
[a]Men/women.

Although all classifications of dyslipidemia resulted in an increased risk for survivors compared to the reference cohort, they also translated into a substantial variation in prevalence. The diversity in applied classifications in literature may contribute to the great variation in reported prevalence of dyslipidemia in CCS (Table 1), however, differences in demographics, assessment methods, and general population risk impede a full comparison between studies. An important result from the current study is that survivors, compared to the reference cohort, exhibited a significantly higher prevalence of treatment with lipid-lowering agents and/or high triglycerides, low HDL-c, high total cholesterol, and high apolipoprotein-B levels, while the prevalence of high LDL-c levels was not significantly different. It is generally known that high levels of triglycerides are an independent risk factor for CVD, although its direct causal relation is hard to prove since elevated triglycerides is often associated with a decreased HDL-c. Low HDL-c is stated an independent risk factor for CVD, although the direct causal role is still uncertain and therapies targeting HDL-c increase have not proven any added value in preventing CVD.[35] For LDL-c, each 1 mmol/L reduction has been associated with 19% relative risk (RR) reduction in major vascular events in the general population.[36] However, not only absolute lipid values seem to contribute to an increased cardiovascular risk, but lipoprotein composition as well[37,38]: Malhotra et al. showed normal mean LDL-c levels in their cohort of ALL survivors, but simultaneously a higher prevalence of an atherogenic LDL-c profile (ie, small dense LDL-c instead of larger particles).[38] The inverse association between CCS and high LDL-c levels in the analyses excluding participants with lipid-lowering agents could likely be explained by both selection and collider bias. Survivors may inherently not only be at a higher risk of dyslipidemia, but survivors might also be more likely to receive treatment for dyslipidemia, as they are more regularly screened compared to the general population.

Recent studies in the general population indicate that Apo-B may be a valuable biomarker with a superiority over HDL-c and LDL-c in predicting CVD.[37,39] Apo-B particles are found to be the main cause of atherosclerosis when they enter and get entrapped into the arterial wall, causing and sustaining the atherosclerotic process. While other lipid biomarkers are only showing the concentration of a composition of these particles, Apo-B reflects the exact number of atherogenic particles. Sniderman et al. showed that Apo-B was the most potent predictor of cardiovascular risk in the general population (standardized relative risk ratio (RRR) = 1.43, 95% CI = 1.35-1.51), in contrast to LDL-c, being the least potent predictor (RRR = 1.25, 95% CI = 1.18-1.33).[39] This growing body of evidence suggests that determining Apo-B might be advantageous in the diagnostic process of dyslipidemia in CCS. However, prospective research is needed to validate Apo-B as a predictive marker for CVD in CCS and to embed it into a validated risk assessment tool.

The current study revealed several determinants of dyslipidemia in CCS that could aid the identification of high-risk patients and the development of targeted interventions. First, we identified survivors previously treated with cranial irradiation (1-25 Gy) to have an over 2-fold increased odds of dyslipidemia (according the NCEP-ATP-III), while survivors receiving >25 Gy did not exhibit this increased risk. This is conceivably due to the fact that the first group mainly consisted of CCS receiving global cranial (-spinal) RT. The 1-25 Gy group consisted almost exclusively of survivors of hematologic malignancies (99.0%), whereas the >25 Gy group had a more heterogeneous survivor population (55.6% CNS tumors, 29.6% solid tumors, 14.3% hematologic malignancies, 0.5% other). Global cranial irradiation has been shown to damage the hypothalamic-pituitary axis, thereby inducing multiple hormone deficiencies,[40] subsequently inducing obesity and dyslipidemia. Additionally, subsequent altered levels of certain key hormones, such as thyroid hormones, play a significant role in lipid metabolism.[41,42] The survivors with highest dosages more typically received local RT to a specific site in the brain, therefore less frequently involving the

Table 8. Treatment and comorbidity related determinants for dyslipidemia (according NCEP-ATP-III and CTCAE v4.03) using multivariable logistic regression analysis.

	NCEP-ATP-III Treatment-related OR (95% CI)	CTCAE v4.03, grade ≥1 Treatment-related OR (95% CI)	NCEP-ATP-III Comorbidity related OR (95% CI)	CTCAE v4.03, grade ≥1 Comorbidity-related OR (95% CI)
Sex (female)	**3.03 (2.06-4.49)**	0.88 (0.56-1.39)	**2.56 (1.77-3.72)**	0.75 (0.49-1.14)
Age (outpatient clinic visit)				
18-29 y	REF	REF	REF	REF
30-39 y	**1.55 (1.04-2.33)**	**1.65 (1.10-2.50)**	**1.77 (1.21-2.58)**	**1.82 (1.25-2.67)**
>40 y	1.70 (0.98-2.95)	**2.64 (1.49-4.71)**	**1.87 (1.11-3.15)**	**3.02 (1.77-5.19)**
Follow-up time (per year)	1.00 (0.97-1.02)	**1.02 (1.00-1.05)**	1.00 (0.97-1.02)	1.02 (0.99-1.04)
BMI (per point)	**1.16 (1.13-1.20)**	**1.10 (1.07-1.14)**	**1.14 (1.11-1.17)**	**1.08 (1.05-1.11)**
Low physical activity (yes vs no)	1.25 (0.96-1.62)	**1.42 (1.08-1.88)**	1.26 (0.98-1.61)	**1.43 (1.10-1.85)**
Smoking (yes vs no)	–	1.20 (0.92-1.57)	–	1.20 (0.94-1.54)
Treatment characteristics				
Abdominal/Pelvic RT (Gy)				
0	REF	REF	–	–
1-30	0.83 (0.46-1.48)	1.30 (0.70-2.39)	–	–
>30	**2.41 (1.28-4.60)**	**2.71 (1.40-5.36)**	–	–
Cranial RT (Gy)				
0	REF	REF	–	–
1-25	**2.07 (1.30-3.32)**	**2.32 (1.42-3.83)**	–	–
>25	1.29 (0.77-2.14)	**1.74 (1.03-2.95)**	–	–
TBI (yes vs no)	**7.81 (4.13-15.35)**	**5.96 (3.02-12.15)**		
Alkylating agents (CED, mg/m^2)				
0	REF	REF	–	–
1-4000	1.15 (0.83-1.59)	0.92 (0.61-1.37)	–	–
4000-8000	**1.44 (1.01-2.05)**	**1.68 (1.12-2.51)**	–	–
>8000	**1.97 (1.43-2.72)**	1.11 (0.77-1.60)	–	–
Corticosteroid (mg/m^2)				
0	REF	REF	–	–
1-10,000	0.84 (0.64-1.11)	0.73 (0.53-1.00)	–	–
>10,000	0.77 (0.41-1.41)	0.68 (0.36-1.29)	–	–
Anthracycline (mg/m^2)[a]				
0	–	REF	–	–
0-200	–	1.38 (0.94-2.03)	–	–
200-400	–	1.39 (0.95-2.01)	–	–
400+	–	1.36 (0.85-2.18)	–	–
Comorbidities				
Diabetes mellitus (yes vs no)	–	–	**4.32 (2.18-9.22)**	**3.28 (1.63-6.96)**
GHD (yes vs no)	–	–	**1.74 (1.05-2.90)**	**1.73 (1.04-2.90)**
Hyperthyroidism (yes vs no)	–	–	**2.43 (1.10-5.66)**	–
Hypogonadism (yes vs no)	–	–	1.48 (0.89-2.46)	1.56 (0.92-2.65)
Interaction terms sex: age				
Female: age group 30-40 y	**0.34 (0.20-0.56)**	**0.43 (0.24-0.77)**	**0.33 (0.20-0.54)**	**0.49 (0.29-0.84)**
Female: age group >40 y	**0.38 (0.20-0.71)**	**0.44 (0.23-0.87)**	**0.44 (0.24-0.79)**	0.56 (0.30-1.06)

Significant values ($P < 0.05$) are displayed in bold.
Models were adjusted for all variables included in the model. Cells denoted by "–" indicate that we did not include this variable in the model. Due to the high number of missing values of the determinant low physical activity (18.9% and 51.3% missing in age groups <40 y and >40 y, respectively), the multivariable models without low physical activity are shown in Table S10.
Abbreviations: NCEP-ATP-III, National Cholesterol Education Program Adult Treatment Panel III; CTCAE v4.03, Modified version of the NCI Common Terminology Criteria for Adverse Events; OR, odds ratio; CI, confidence interval; y, year; REF, reference; BMI, body mass index; RT, radiotherapy; Gy, gray; TBI, total body irradiation; CED, Cyclophosphamide equivalent dose; GHD, growth hormone deficiency.

hypothalamus and pituitary in the radiation field. Whereas cranial RT was significantly associated with dyslipidemia for all separate lipid abnormalities and classifications used in multivariable logistic regression analysis, abdominal RT (>30 Gy) was only associated with certain outcome definitions (high triglycerides, NCEP-ATP-III, and CTCAE v4.03, grade ≥1). Previous reports showed nephroblastoma and neuroblastoma survivors to have higher triglycerides, but also higher LDL-c and free fatty acid levels, which was hypothesized to be related to radiation-induced damage on individual organs (ie, pancreas, liver).[43] Additionally, altered body composition (ie, increased abdominal fat) has been found to be an important factor in the increased dyslipidemia risk after abdominal RT.[44]

Hypogonadism following cancer treatment (including after abdominal RT[45] and alkylating agents[45,46]) is often reported[45] and some CCS studies reported associations with both overweight and dyslipidemia.[40] Obese CCS carry an significant increased risk of dyslipidemia (OR = 1.04 (95% CI = 1.02-1.08) - 1.16 (95% CI = 1.12-1.20) per BMI point in our models), as fat tissue plays an important role through the release of free fatty acids and therefore increases triglyceride and LDL-c production in the liver.[47] Nevertheless, sex hormones themselves also appear to have a direct link to lipid metabolism.[41] In our univariable analysis, hypogonadism was significantly associated with dyslipidemia, however, this association did not reach significance in our multivariable models. As we defined hypogonadism by ever having been diagnosed with hypogonadism in medical charts, a conceivable underestimation of its true prevalence may have been induced. This was illustrated in the work by Hudson et al., where screening (including laboratory tests) for conditions such as Leydig cell failure and primary ovarian failure revealed a substantially higher prevalence compared to data based solely on medical record abstraction.[24]

Finally, as we identified BMI, physical activity, smoking, and diabetes mellitus to be associated with (at least one definition of) dyslipidemia, we emphasize the importance of implementing lifestyle interventions in our high-risk CCS population, ultimately inducing a more favorable lipid profile and hence a possible lower risk of CVD.

When interpreting our results, some limitations need to be considered. The limited participation rate and observed differences between characteristics of participants and non-participants could indicate selection bias, although absolute differences were small. Unfortunately, dosimetry data was not available yet in the current study and the association between radiation dose on risk organs and dyslipidemia needs to be explored in further studies. Additionally, our data on low physical activity contained a substantial number of missing values, possibly resulting in less robust models. Therefore, we also estimated the models without this variable which showed similar results. Lastly, the current study lacked an association analysis between dyslipidemia and the risk of cerebrovascular and CVD, which we feel would be unfeasible, given the current young median age of our cohort. Nevertheless, this association is already well established in the general population[5] and has been reported in CCS as well.[8]

In conclusion, our national CCS cohort with long-term follow-up revealed a high prevalence of dyslipidemia and high prevalence of lipid-lowering agents use at an already young adult age. Although the different definitions of dyslipidemia translated into substantial differences in prevalence, all classifications revealed an increased risk of dyslipidemia in survivors compared to the general population. Sex, age, BMI, physical activity, smoking, prior abdominal/pelvic RT, cranial RT, total body irradiation, alkylating agents, growth hormone deficiency, and diabetes mellitus are associated with dyslipidemia risk in CCSs. As the current cardiovascular assessment tools are not fully applicable to CCS, further research is needed to provide survivor-specific risk assessment tools, including treatment exposures and lipid biomarker thresholds, to prevent and control the cerebrovascular and cardiovascular morbidity and mortality in this high-risk population.

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Supplementary material

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Authors' contributions

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Data availability

The data underlying this article were provided by the DCCSS-LATER consortium under license. Data will be shared on reasonable request to the corresponding author with permission of the DCCSS-LATER consortium. The data are not publicly available due to privacy or ethical restrictions. Concerning the data of the Lifelines cohort, data may be obtained from a third party and are not publicly available. Researchers can apply to use the Lifelines data used in this study. More information about how to request Lifelines data and the conditions of use can be found on their website (https://www.lifelines.nl/researcher/how-to-apply).

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