**Supplementary data:**

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

Faber J1\*, Wingerter A1\*, Neu MA1, Henninger N1, Eckerle S1, MünzelT2,3, Lackner KJ4, Beutel ME5, Blettner M6, Rathmann W7, Peters A8,9,10, Meisinger C9,11, Linkohr B9, Neuhauser H12,13, Kaatsch P14, Spix C14, Schneider A6, Merzenich H6, Panova-Noeva M15,16, Prochaska JH3,15,16,17, Wild PS3,15,16,17

*\* These authors contributed equally to this work.*

1Department of Pediatric Hematology/Oncology/Hemostaseology, Center for Pediatric and Adolescent Medicine, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

2Center for Cardiology – Cardiology I, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

3German Center for Cardiovascular Research (DZHK) Partner Site Rhine-Main, Mainz, Germany

4Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

5Clinic for Psychosomatic Medicine and Psychotherapy, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

6Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

7Department of Biometry and Epidemiology, German Diabetes Center, Düsseldorf, Germany

8German Center for Cardiovascular Disease Research (DZHK), Partner Site Munich, Munich, Germany

9Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

10Institute for Cardiovascular Prevention, Ludwig-Maximilian-University Hospital, Munich, Germany

11KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Augsburg, Germany

12Department of Epidemiology and Health Monitoring, Robert Koch Institute, Berlin, Germany

13German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany

14German Childhood Cancer Registry (GCCR), Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

15Center for Thrombosis and Haemostasis, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

16Center for Translational Vascular Biology (CTVB), University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

17Preventive Cardiology and Preventive Medicine, Centre for Cardiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

**Corresponding author:**

Univ.-Prof. Dr. med. Joerg Faber

University Medical Center Mainz
Department of Pediatric Hematology/Oncology/Hemostaseology

Langenbeckstraße 1
55131 Mainz, Germany

Phone: +49 6131 17 6821

Fax: +49 6131 17 5548

Email: faber@uni-mainz.de

**Table S1:** Measurement and definition of cardiovascular risk factors in the CVSS-study cohort

|  |  |
| --- | --- |
| **CVRF** | **Definition/measurement** |
| Arterial hypertension | - Intake of antihypertensive medication within the past two weeks (CAPI, medical records and medication packages)*and/ or*- Mean systolic blood pressure of ≥ 140 mmHg and/ or mean diastolic blood pressure of ≥ 90 mmHg at rest in a three-time measurement in a sitting position after 5, 8 and 11 minutes (values reported corresponding to the average of the second and the third measurement)  |
| Dyslipidaemia | - Physician´s diagnosis (CAPI, medical records)*and/ or* - LDL/HDL ratio > 3.5 and/ or a fasting blood triglyceride level ≥ 150 mg/dl |
| Obesity |  - Body mass index (BMI) ≥ 30 kg/m² |
| Diabetes mellitus | - Physician`s diagnosis of any type of diabetes (CAPI, medical records) *and/ or* - Intake of antidiabetic medication within the past two weeks (CAPI, medical records, medication packages)*and/ or* - HBA1c ≥ 6.5% |
| Smoking  | - Occasional and regular daily smokers (CAPI) |
| Positive family history for myocardial infarction and/ or stroke | - At least one reported first-degree relative with myocardial infarction or stroke at age ≤ 60 years (men) or ≤ 65 years (women) (CAPI) |
| Metabolic syndrome | At least 3 of the following 5 parameters:- Waist circumference ≥ 94 cm (men), ≥ 80 cm (women)- Fasting blood triglyceride level ≥ 150 mg/dl *and/ or* medication for elevated triglycerides- Reduced HDL level ≤ 40 mg/dl (men), ≤ 50 mg/dl (women) *and/ or* medication for reduced HDL- Elevated blood pressure (systolic ≥ 130 mmHG *and/ or* diastolic ≥ 85 mmHg *and/or* antihypertensive medication)- HBA1c ≥ 6.5% *and/ or* physician´s diagnosis *and/ or* antidiabetic medication |

CAPI = Computer-assisted personal interview, CVRF = Cardiovascular risk factor,

HBA1c = Glycated haemoglobin A1c, HDL = High-density lipoprotein, LDL = Low-density lipoprotein

**Table S2:** Demographic characteristics of the CVSS-study sample and the comparison cohorts (GHS, DEGS, KORA)

a)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CVSS-study** **N=**951 | **GHS****N=**8695 | **DEGS****N=**2915 | **KORA****N=**2034 |
|  | N (%) | N (%) | N (%) | N (%) |
| **Age at examination (years)** |  |  |  |  |
| 20-24  | 11 (1.2) |  | 158 (5.4) | 7 (0.3) |
| 25-29  | 216 (22.7) |  | 440 (15.1) | 319 (15.7) |
| 30-34  | 299 (31.4) |  | 469 (16.1) | 512 (25.2) |
| 35-39 | 256 (26.9) | 1468 (16.9) | 533 (18.3) | 456 (22.4) |
| 40-44 | 122 (12.8) | 1716 (19.7) | 686 (23.5) | 403 (19.8) |
| 45-4950-5455-59 | 47 (4.9) | 1874 (21.6)1896 (21.8)1741 (20.0) | 629 (21.6) | 337 (16.6) |
| **Sex** |  |  |  |  |
| Female | 425 (44.7) | 4279 (49.2) | 1,553 (53.3) | 1062 (52.2) |
| Male | 526 (55.3) | 4416 (50.8) | 1,362 (46.7) | 972 (47.8) |

b)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CVSS-study** **N=**951 | **GHS****N=**8695 | **DEGS****N=**2915 | **KORA****N=**2034 |
| **Age at examination** **(mean, SD)[years]** | 34.0 (5.6) | 47.4 (7.0) | 37.3 (7.5) | 36.7 (6.5) |
| **Period of data assessment** | 2013-2016 | 2007-2012 | 2008-2011 | 1999-2001 |

CVSS = Cardiac and vascular late sequelae in long-term survivors of childhood cancer, DEGS = German Health Interview and Examination Survey for Adults, GHS = Gutenberg Health Study, KORA = Cooperative Health Research in the region of Augsburg, SD = Standard deviation

**Table S3:** Continuous measures of cardiovascular risk factors among CVSS-study participants (N=951)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Mean / Standard deviation** | **Median (Q1/Q3)** | **Minimum** | **Maximum** |
|  |  |  |  |  |  |
| **Cardiovascular risk factor** |  |  |  |  |  |
| Body mass index (BMI) |  | 25.9 / ±5.3 | 24.9 (22.2/28.3) | 14.6 | 52.1 |
| Waist circumference | cm | 87.9 / ±13.8 | 86.6 (78.0/95.9) | 57.7 | 173.5 |
| High-density lipoprotein (HDL) | mg/dl | 55.2 / ±15.3 | 53.0 (44.0/64.0) | 19.0 | 123.0 |
| Low-density lipoprotein (LDL) | mg/dl | 131.2 / ±34.6 | 127.0 (107.0/152.0) | 22.0 | 284.0 |
| Lipids ratio (LDL/HDL) |  | 2.6 / ±1.0 | 2.4 (1.8/3.1) | 0.3 | 7.7 |
| Triglycerides | mg/dl | 119.1 / ±90.9 | 98.0 (72.0/137.0) | 26.0 | 1341.0 |
| Systolic blood pressure | mmHg | 123.0 / ±13.0 | 122.0 (113.5/131.0) | 87.5 | 185.0 |
| Diastolic blood pressure | mmHg | 79.9 / ±9.2 | 79.5 (73.5/85.5) | 51.5 | 119.5 |

CVSS = Cardiac and vascular late sequelae in long-term survivors of childhood cancer

**Table S4:** Age at examination and the prevalence of cardiovascular risk factors and cardiovascular disease among the CVSS-study participants according to ICCC 3 diagnoses and sex (without adjustment for age)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | **All** | **Age at examination** | **CVD** | **VTE** | **CHF** | **Arterial hypertension** | **Obesity** | **Dyslipidemia** | **Diabetes mellitus** | **Smoking** | **FH** |
|   | % (N) | Mean (SD)) | % (N) | % (N) | % (N) | % (N) | % (N) | % (N) | % (N) | % (N) | % (N) |
| All | 951 | 34.6 (5.5) | 4.5 (43)b | 2.0 (19)a | 1.2 (11)a | 23.0 (219)a | 17.4 (165)a | 28.3 (269)a | 2.0 (19)a | 21.5 (204)a | 19.7 (187)c |
| **ICCC3 diagnosis** |   |   |   |   |   |   |   |   |   |   |   |
| Leukaemia | 43.5 (414) | 34.3 (5.1)  | 3.1 (13 )a | 1.5 (6)a | 0.5 (2)a | 20.1 (83)a | 19.3 (80) | 21.5 (89)a | 1.5 (6) | 23.2 (96)a | 21.7 (90)c |
| Lymphoma | 9.9 (94) | 37.5 (4.6) | 3.2 (3) | 1.1 (1) | 1.1 (1) | 31.9 (30) | 18.1 (17) | 42.6 (40)b | 2.1 (2) | 25.5 (24) | 22.3 (21)c |
| CNS tumours  | 12.8 (122) | 35.5 (5.2) | 6.6 (8)b | 4.1 (5) | 0 (0) | 19.7 (24) | 20.5 (25) | 36.9 (45)a | 3.3 (4) | 19.7 (24)a | 18.0 (22)c |
| Sympathetic nervous system tumours | 7.6 (72) | 29.7 (4.1) | 2.8 (2)b | 1.4 (1) | 0 (0) | 20.8 (15) | 13.9 (10) | 25.0 (18)b | 2.8 (2) | 26.4 (19) | 11.1 (8)c |
| Retinoblastoma | 1.1 (10) | 29.2 (4.8) | 0 (0) | 0 (0) | 0 (0) | 20.0 (2) | 10.0 (1) | 30.0 (3 ) | 0 (0) | 50 (5) | 10.0 (1) |
| Renal tumours | 8.1 (77) | 32.8 (3.9) | 7.8 (6)b | 2.9 (3) | 2.6 (2) | 18.2 (14) | 14.3 (11) | 20.8 (16)b | 2.6 (2) | 16.9 (13) | 16.9 (13)b |
| Hepatic tumours | 0.7 (7 ) | 28.4 (2.0) | - (0) | 0 (0) | 0 (0) | - (0) | - (1) | - (1) | 0 (0) | - (1) | - (1) |
| Malignant bone tumours | 5.3 (50) | 40.6 (4.5) | 8.0 (4)b | 2.0 (1) | 4.0 (2) | 42 (21) | 10.0 (5) | 42 (21) | 4.0 (2) | 18.0 (9) | 32.0 (16)c |
| Soft tissue sarcomas  | 7.5 (71) | 34.3 (6.2) | 8.5 (6)b | 2.8 (2) | 5.6 (4) | 36.6 (26) | 18.3 (13) | 33.8 (24) | 1.4 (1) | 11.3 (8) | 16.9 (12)c |
| Germ cell tumours | 2.7 (26) | 33.8 (7.4) | 3.9 (1)c | 0 (0) | 0 (0) | 11.5 (3) | 3.9 (1) | 34.6 (9) | 0 (0) | 15.4 (4) | 7.7 (2)b |
| Carcinoma | 0.7 (7) | 37.0 (8.5) | 0 (0) | 0 (0) | 0 (0) | - (1) | - (1) | - (3) | 0 (0) | - (0) | - (1)b |
| Other | 0.1 (1) | 33.7 (-) | 0 (0) | 0 | 0 | 0 (0) | 0 (0) | 0 | 0 | - (1) | 0 |
|   |   |   |   |   |   |   |   |   |   |   |   |
| **Sex** |   |   |   |   |   |   |   |   |   |   |   |
| female | 44.7 (425) | 34.0 (5.6) | 6.6 (28)b | 3.3 (14)a | 1.7 (7)a | 17.9 (76)a | 19.5 (83) | 18.6 (79)b | 2.6 (11) | 19.8 (84)a | 18.4 (78)c |
| male | 55.3 (526) | 35.0 (5.5) | 2.9 (15)b | 1.0 (5) | 0.8 (4) | 27.2 (143) | 15.6 (82) | 36.1 (190)a | 1.5 (8) | 22.8 (120)a | 20.7 (109)b |

CHF = Congestive heart failure, CVD = Cardiovascular disease, CVSS = Cardiac and vascular late sequelae in long-term survivors of childhood cancer, FH = Positive family history for myocardial infarction/ stroke, ICCC 3 = International classification of childhood cancer, CNS = Central nervous system, SD = Standard deviation, VTE = Venous thromboembolism, a = <1% missings, b = <5% missings, c = < 10% missings

**Table S5:** Intake of drugs among the CVSS-study sample and comparison with DEGS and KORA samples after weighting for the age and sex distribution of the CVSS-study sample

a)

|  |  |
| --- | --- |
|  | **CVSS-study** |
|  | % (N) |
|  |  |
| **Intake of Drugs** |  |
| Any drug intake (ATC) | 69.3 (659) a |
| Genitourinary system and reproductive hormones (ATC-G) | 20.4 (194) a |
| Musculoskeletal system (ATC-M) | 18.7 (178) a |
| Systemic hormonal preparations, excluding reproductive hormones and insulins (ATC-H) | 18.1 (172) a |
| Nervous system (ATC-N) | 18.0 (171) a |
| Respiratory system (ATC-R) | 17.9 (170) a |
| Alimentary tract and metabolism (ATC-A) | 16.6 (158) a |
| Various ATC structures (ATC-V) | 13.8 (131) a |
|  Cardiovascular system (ATC-C) | 11.0 (105) a |
| Dermatological drugs (ATC-D) | 10.2 (97) a |
| Sensory organs (ATC-S) | 5.1 (48) a |
| Antiinfectives for systemic use (ATC-J) | 3.7 (35) a |
| Drugs used in diabetes (ATC-a10) | 1.0 (9) a |
| Antineoplastic and immunomodulating agents (ATC-L) | 0.6 (6) a |
| Antiparasitic products, insecticides and repellents (ATC-P) | 0.2 (2) a |

b)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CVSS-study** | **DEGS** | **KORA** |
|  | % (N) | % (N) | % (N) |
|  Any drug intake (ATC) | 69.3 (659)a  | 56.5 (1536)a | 46.5 (996)a |
|  Cardiovascular system (ATC-C) | 11.0 (105)a | 5.9 (221)a | 4.2 (123)a |
| Drugs used in diabetes (ATC a10)  | 1.0 (9)a | 0.8 (28)a | 0.7 (19)a |
| Cardiovascular system and/ or drugs used in diabetes (ATC C and/or ATC a10)  | 11.8 (112)a | 6.4 (237)a | 4.7 (135)a |

ATC = Anatomical Therapeutic Chemical classification system of the World Health Organization Collaborating Centre for Drug Statistics Methodology, CVSS = Cardiac and vascular late sequelae in long-term survivors of childhood cancer, DEGS = German Health Interview and Examination Survey for Adults, KORA = Cooperative Health Research in the region of Augsburg, a = <1% missings