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Metabolic syndrome as cardiovascular risk factor in childhood cancer survivors

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ABSTRACT

Over the past decades, survival rates of childhood cancer have increased considerably from 5 to 30% in the early seventies to current rates exceeding 80%. This is due to the development of effective chemotherapy, surgery, radiotherapy and stem cell transplantation, combined with an optimized stratification of therapy and better supportive care regimens. As a consequence, active surveillance strategies of late sequelae have been developed to improve the quality of survival. Several epidemiological studies have reported an increased incidence of (components of) metabolic syndrome (MetS) and cardiovascular disease in childhood cancer survivors (CCS). Growth hormone deficiency (GHD) after cranial radiotherapy (CRT) has been previously described as an important cause of MetS. New insights suggest a role for abdominal radiotherapy as a determinant for MetS as well. The role of other risk factors, such as specific chemotherapeutic agents, steroids, gonadal impairment, thyroid morbidity and genetics, warrants further investigation. This knowledge is important to define subgroups of CCS that are at risk to develop (subclinical) MetS features. These survivors might benefit from standard surveillance and early interventions, for example lifestyle and diet advice and medical treatment, thereby preventing the development of cardiovascular disease.

1. Introduction

Over the past decades, survival rates of childhood cancer have increased considerably from 5 to 30% in the early seventies to current rates exceeding 80% (Howlader et al., 2016). This is due to the development of effective chemotherapy, surgery, radiotherapy and stem cell transplantation (SCT), combined with an optimized stratification of therapy and better supportive care regimens. These improved survival rates currently result in an ongoing increasing number of survivors (Meadows, 2003), which in turn resulted in increased awareness of late side effects of treatment for childhood cancer, and research investigating these late sequelae.

Several epidemiological studies have reported an increased incidence of cardiovascular disease in survivors of childhood cancer (Supplemental table 1). Standardized mortality risk, e.g. due to stroke and coronary heart disease, ranges from 1.9 to 12.7, with higher risk for specific subgroups with regard to diagnosis, administered treatment and follow-up time (Reulen et al., 2010; Tukenova et al., 2010; Castellino et al., 2011; Prasad et al., 2012; Armstrong et al., 2013; Perkins et al., 2013; Kero et al., 2014; van Laar et al., 2014; Olsen et al., 2014; Kero et al., 2015; Gudmundsdottir et al., 2015; Bhakta et al., 2016; Schindler et al., 2016; Kero et al., 2016a).

The pathophysiology of the development of cardiovascular disease in childhood cancer survivors is a multifactorial process as in the normal population, but with additional treatment and disease specific modulators. Frequently reported risk factors for cardiovascular sequelae are adiposity, insulin resistance/diabetes mellitus, dyslipidemia and hypertension, which cluster as the entity "metabolic syndrome" (van Waas et al., 2010; Rosen et al., 2013; Casco and Soto-Vega, 2016). This narrative review summarizes existing literature on the frequency and determinants of metabolic syndrome and its components in childhood cancer survivors.

2. Methods

We searched PubMed and Embase for the following terms and synonyms: "childhood cancer survivor", "metabolic syndrome", "obesity", "insulin resistance", "diabetes", "dyslipidemia" and "hypertension".

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Table 1a
Overweight and obesity in childhood cancer survivors.

Author	Year	N	Population	Design	Follow-up	% Overweight	% Obese	MVA	Prognostic variable
Zhang†	2014	1742	ALL	1	< 10y	Meta-analysis BMI Z-score 0.83 (80th percentile)*	n.a.	Meta-analysis	None, high prevalence of obesity among survivors independent of patient and treatment characteristics
Moustoufi†	2016	13203	CCS	2	24y Mdn (5-39y)	n.a.	12-25	Yes	CRT > 18 Gy, TBI, Abd RTx (among survivors); CRT < 18 Gy less obesity (compared to siblings)
Belle†	2018	2365	CCS	2	15y Mdn (IQR 3-9y)	26	n.a.	Yes	CRT > 20 Gy
Wilson†	2015	1996	CCS	2	24.6y Mdn (10.7-48.3y)	27.9	36.2	Yes	CRT, glucocorticoids, older age at evaluation; abdominal, chest, pelvic radiation less obesity
Van Santen†	2015	893	CCS	2	14.9y M (4.7-36.2y)	23.3	n.a.	Yes	CRT, younger age at diagnosis, high BMI at diagnosis
Brown†	2016	406	ALL	2	11.39y M (± 5.33y)	27.6	22.2	Yes	CRT, Hispanic
Felicetti†	2015	330	CCS	2	16.1y Mdn (5.1-33.0y)	n.a.	8	Yes	Brain tumor, anthracyclines, older age at diagnosis
Prasad†	2015	648 (471 < 18y)	CCS	3	6y Mdn (2-16y) (< 18y); 11.5y Mdn (2-41y) (≥18y)	10.8 (< 18y); 8.5 (≥18y)	2.7 (< 18y); 0 (≥18y)	Yes	ALL, brain tumor
Gunn†	2016	276	CCS	3	n.a.	32.3	n.a.	Yes	CRT
Lindemulder†	2015	269	ALL CRT-	3	9.1y Mdn (4.8-13.7y)	18.1	20.9	Yes	n.a.
Essig	2014	556	ALL	2	18.4y Mdn (0.0-33.0y)	n.a.	21	No	n.a.
Stolley	2015	452	CCS	2	18.4y (± 9.3)/16.7y (± 6.8)/20.2 (± 7.9)** M	n.a.	32 / 42 / 23**	No	Hispanic, African-American
Berdan	2014	413	CCS	2	18.5y M (± 8.1y)	28.9	32.4	No	Hispanic
Brouwer	2013	277	CCS	2	18y Mdn (5-31y)	33	n.a.	No	n.a.
Nayjager	2017	75	ALL	2	15.07y Mdn (10.22-26.30y)	25.3	8	No	n.a.
Latoch	2016	75	CCS	2	12.15y Mdn (1-23.5y)	29.3	n.a.	No	n.a.
Siviero	2013	56	ALL	2	8.5y M (± 3.9y)	n.a.	3.6	No	n.a.
Murphy	2015	53	CCS	2	Range 3.2-14.4y	0	n.a.	No	n.a.
Jahnukainen	2015	49	ALL male	2	20y Mdn (10-29y)	n.a.	15	No	Cranial/testicular radiation (NS)
Van Dorp	2013	191	CCS female	3	18.8y Mdn (2.3-48.8y)	13	10	No	n.a.
Shalitin	2014	139	Non-brain solid	3	9y Mdn (1.2-29.5y)	n.a.	1.4	No	n.a.
Harper	2013	27	ALL RTx-	3	6y	40.7	n.a.	No	n.a.

† Highest quality evidence, based on design (1 = meta-analysis, 2 = cross-sectional, 3 = retrospective) and MVA (multivariable analysis).
* Meta-analysis calculated overall BMI Z-score and corresponding BMI percentile.
** Three separated groups: African-American, Hispanic, Non-Hispanic White.
ALL = acute lymphoblastic leukemia; CCS = childhood cancer survivors; M = mean; Mdn = median; CRT = cranial radiotherapy; TBI = total body irradiation; Abd RTx = abdominal radiotherapy; NS = not significant; n.a. = not available.

3. Components of the metabolic syndrome in childhood cancer survivors

3.1. Overweight, obesity and adiposity

Overweight, obesity and adiposity are frequently described phenomena in CCS. Overweight is defined as body mass index (BMI) ≥25 and < 30 kg/m2, obesity as BMI ≥ 30 kg/m2. Population based, the prevalence of overweight has increased enormously over the past decades, especially in developed countries. In 2014, an estimated 1.9 billion adults (i.e. 39% of the adult population worldwide), suffered from overweight, of which a third was obese (WHO, 2017a). Overweight has a negative influence on blood pressure, lipid metabolism and insulin resistance. A five kg/m^2 (Meadows, 2003) BMI increase has been described to be associated with a 1.5- or 2-fold risk increase for coronary heart disease, and 4- or 8-fold for diabetes mellitus (Willett et al., 1999). Also, overweight enhances the risk of stroke (1.3-fold (Walker et al., 1996)) and of several types of cancer, e.g. postmenopausal breast, colon, thyroid, renal, endometrium and esophageal, with a relative risk of 1.12–1.59 per 5 points BMI increase (Renehan et al., 2008).

Adiposity is a broader term including more accurate measurements of adipose tissue accumulation, such as waist circumference, waist/hip ratio and sometimes fat percentage or body composition (assessed by Dual-energy X-ray Absorptiometry [DXA]) (Nysom et al., 1999; Nysom et al., 2001; van Beek et al., 2006; Neville et al., 2006; Jarfelt et al., 2005; Janiszewski et al., 2007; Blijdorp et al., 2012). There is increasing evidence that BMI values reflect underestimations of adiposity, and that the accumulation of visceral fat as well as body composition as measured by DXA are more reliable measures for overweight to predict the development of cardiovascular disease (Blijdorp et al., 2012; Shuster et al., 2012; Fox et al., 2007; Mostoufi-Moab et al., 2012; Siviero-Miachon et al., 2013; van Waas et al., 2012; Marriott et al., 2017). However, since DXA is a time consuming, financially less attractive diagnostic test which, in addition, requires low dose radiation in children who have often already been exposed to teratogenic treatments, BMI is the most commonly used tool to study overweight.

The first reports on overweight risk after childhood cancer were published in the eighties, initiated by the impression that many survivors of childhood leukemia were overweight or obese (Zee and Chen, 1986). A correlation with CRT, often associated with growth hormone deficiency (GHD), was reported, which was confirmed in consecutive studies thereafter (Nysom et al., 1999; Blijdorp et al., 2012; Odame et al., 1994; Sklar et al., 2000). Subsequently, further detailed studies pointed out that the risk of overweight was especially high among female survivors and survivors diagnosed at younger age and was radiation dose- and site-dependent (Oeffinger et al., 2003; Garmey et al., 2008; Mostoufi-Moab et al., 2016; Wilson et al., 2015). On the other hand, a recent meta-analysis in 1742 ALL survivors reported a high prevalence of overweight – 80th BMI percentile –, independent of patient and treatment characteristics (Zhang et al., 2014). Nine recently published studies performed multivariable analysis to describe independent risk factors for overweight, six of which had a cross-sectional design, and three were retrospective studies (Mostoufi-Moab et al., 2016; Wilson et al., 2015; van Santen et al., 2015; Brown et al., 2016; Felicetti et al., 2015; Prasad et al., 2015; Lindemulder et al., 2015; Gunn et al., 2016; Belle et al., 2018). The largest is a report from the Childhood Cancer Survivor Study (CCSS), comparing self-reported overweight between 13,000 survivors, after median 24 years' follow-up, and 4000 siblings in 27 participating centers in the United States and Canada (Mostoufi-Moab et al., 2016). Overweight rate was the same in both study groups (RR 1.0, 95% CI 0.9–1.1). Among survivors, CRT > 18 Gy, total body irradiation (TBI) and abdominal radiotherapy were independent risk factors for overweight. After a follow up of 24.6 years, the St. Jude Lifetime cohort, consisting of ~2000 patients that underwent late effect surveillance in the After Completion of Therapy (ACT) Clinic, showed a prevalence of obesity of 36%, with a standardized morbidity ratio of 1.14 when compared to matched controls (Wilson et al., 2015). CRT (OR 1.66) and previous glucocorticoids treatment (OR 1.37) as well as older age at evaluation were independent risk factors of becoming obese, whereas previous chest/abdominal/pelvic radiation (OR 0.48) was associated with lower obesity prevalence among survivors. In the Swiss Childhood Cancer Survivor Study, the prevalence of self-reported overweight in 2400 CCS was similar to siblings and the general population, and CRT > 20 Gy was an independent risk factor for overweight among survivors (Belle et al., 2018). The three other studies with a cross-sectional design comprised between 330 and 900 survivors, and reported the following independent risk factors for overweight or obesity: brain tumor, CRT, anthracyclines, high BMI at diagnosis and Hispanic race (van Santen et al., 2015; Brown et al., 2016; Felicetti et al., 2015). In summary, in studies of highest quality, CRT is the most frequently reported independent risk factor of overweight in CCS (Table 1a).

3.2. Insulin resistance and type II diabetes mellitus

Diabetes mellitus (DM) gives rise to the risk of micro- and macrovascular damage (Emerging Risk Factors Collaboration, 2010; WHO and IDF, 2006) (Fig. 1). Type II DM (DM2) is thought to be the result of insulin resistance (IR) and (visceral) adiposity-associated chronic inflammation and, ultimately, pancreatic β-cell dysfunction (Donath and Shoelson, 2011; Tack et al., 2012). It is estimated that worldwide 5,5% of people suffer from DM. As with obesity, the prevalence of DM – especially DM2 – in the general population has increased substantially over the past decades, from 4.7% in 1980 to 8.5% in 2014 (WHO, 2017b). As adiposity is highly associated with the development of fatty liver disease, IR and DM2 (Colditz et al., 1995; Mokdad et al., 2003; Nguyen et al., 2011; Menke et al., 2014), it is anticipated that adipose survivors more frequently suffer from diabetes than non-adipose survivors. In addition, some studies suggest an increased prevalence of diabetes after adjusting for obesity, e.g. due to radiotherapy (Neville et al., 2006; Baker et al., 2007; Meacham et al., 2009; de Vathaire et al., 2012; Cohen et al., 2014).

Table 1b provides an overview of recent literature on IR and DM in CCS. Twenty years ago, the first reports on an increased risk of DM after abdominal radiation in survivors of Wilms tumor were published (Teinturier et al., 1995; Cicognani et al., 1997), suggesting a damaging effect of radiation to the pancreas. From a cross-sectional study in ~8600 survivors by Meacham, the prevalence of self-reported DM after 23.5 years of follow-up was 2.5% in survivors and 1.7% in siblings ($p < 0.01$). Among survivors, this was explained in particular by TBI (OR 7.2), abdominal radiotherapy (OR 2.7), alkylating agents (OR 1.7) and younger age at diagnosis (OR 2.4). No association was found with CRT and corticosteroids (Meacham et al., 2009). Holmqvist retrospectively reported hospitalizations for DM in a large cohort of ~33,000 survivors, ten years after diagnosis. The observed hospitalization rate was 1.6 times higher than expected and especially high in survivors treated with radiotherapy, i.e. Wilms tumor (OR 2.9), leukemia (2.0), CNS tumor (1.8), germ-cell tumor (1.7) and bone tumor (1.7) (Holmqvist et al., 2014). A large cross-sectional study in ~1000 adult survivors treated with HSCT also revealed TBI as an independent risk factor for DM (OR 3.42) (Baker et al., 2007). A study in 750 pediatric HSCT treated survivors added asparaginase toxicity, defined as hyperglycemia and/or pancreatitis, as an independent risk factor (Hoffmeister et al., 2004), and a prospective study in 250 CCS reported TBI and hypogonadism as independent risk factors (Neville et al., 2006). Chao found no significant increase in DM frequency in 650 survivors compared to 6520 non-cancer controls (Chao et al., 2016). In summary, several studies investigated DM in large cohorts of cancer survivors, and radiotherapy – total body as well as abdominal – seems to be the most frequently reported independent risk factor.

The link with damage to the pancreas by radiotherapy was closely investigated by De Vathaire (de Vathaire et al., 2012). Radiation to the

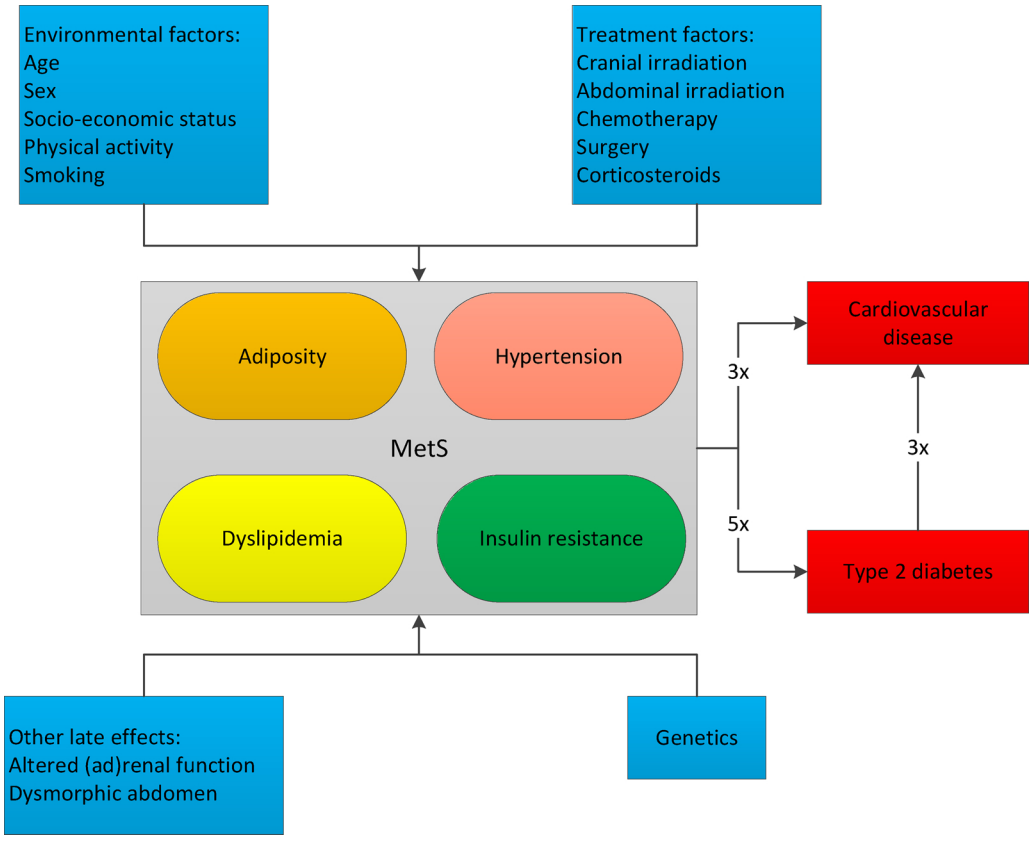

Fig. 1. Metabolic syndrome in childhood cancer survivors and the risk of cardiovascular disease.
The components of the metabolic syndrome, risk factors for developing the syndrome and the risk for metabolic syndrome patients to develop cardiovascular disease and type 2 diabetes (Alberti et al., 2006; Wilson et al., 2005; Ford, 2004).

pancreatic tail, where the majority of insulin-secreting Langerhans islets is located, increased the risk of diabetes in a dose-dependent way (RR at 1 Gy 1.61), whereas the radiation dose to the head or body had no significant effect. A similar dose-dependent relation between radiation to the pancreatic tail and the occurrence of DM was found in adult Hodgkin lymphoma survivors (van Nimwegen et al., 2014). In our study in nephro- and neuroblastoma survivors, radiotherapy to the whole pancreas increased the risk of IR, compared to controls and to radiation to parts of the pancreas (van Waas et al., 2012). A study in ALL survivors reported lower pancreatic volume and insulin secretion after TBI, suggesting a reduced beta cell reserve (Wei et al., 2015). Apart from pancreatic radiation damage impairing insulin secretion, it might be that radiotherapy impairs fat cell expansion, which increases liver steatosis and circulation of free fatty acids (FFA), subsequently causing IR and DM. In mice, it has been shown that adipose tissue fibrosis restricts adipocyte enlargement and is associated with local inflammation and systemic IR (Berryman et al., 2016; Sun et al., 2013). Whether these biological mechanisms determine the higher MetS risk in abdominally irradiated cancer survivors as well, needs to be investigated.

3.3. Dyslipidemia

Classic parameters of dyslipidemia include elevated fasting levels of total cholesterol and low-density lipoprotein cholesterol and triglycerides, and low levels of high-density lipoprotein cholesterol. These alterations in lipid metabolism are associated with cardiovascular disease (Genest et al., 1992; Mora et al., 2011; Parish et al., 2012). Adipose tissue plays an important causal role in the occurrence of dyslipidemia through the release of FFA, which leads to increased triglyceride and very low-density lipoprotein cholesterol production in the liver (Jung and Choi, 2014). Hence, cancer survivors with an increased risk of overweight carry an increased risk of dyslipidemia as well. Hypogonadism following cancer therapy can cause dyslipidemia directly as well; this was observed in survivors of adult testicular cancer (Haugnes et al., 2010; Hashibe et al., 2016), breast cancer treated with aromatase inhibitors (Amir et al., 2011) and prostate cancer treated with LHRH-agonists (Kintzel et al., 2008).

As depicted in Table 1c, the rate of dyslipidemia in CCS varied greatly and different outcome measures are reported. Only one study reported independent risk factors for dyslipidemia in CCS. In 330 survivors, after 16.1 years of follow-up, older age at diagnosis (HR 1.1), TBI (2.7), GHD (2.3) and autologous SCT (3.2) were independent risk factors for hypercholesterolemia, and TBI (6.5) and GHD (7.2) were also independent risk factors for hypertriglyceridemia (Felicetti et al., 2015). Chao studied dyslipidemia in 650 survivors and reported a higher risk (incidence rate ratio 1.9) compared to controls, but no specific prognostic variables were identified in multivariable analysis (Chao et al., 2016). In the CCSS the incidence of dyslipidemia was 8.9%, compared to 6.0% in siblings; this increased to a significant difference at age 50 (23.0 vs 13.6%), whereas the obesity rate at older age in this cohort was significantly higher among siblings (Armstrong et al., 2013). In a large Finnish cohort of ~2500 survivors, the rate of dyslipidemia, defined as the purchase of lipid-lowering drugs, was 4.3 times higher than in siblings (Kero et al., 2016b).

3.4. Hypertension

Arterial hypertension is a condition in which blood pressure is persistently raised, defined as ≥140mmHg systolic or ≥90 diastolic. Globally, the overall prevalence of hypertension in the general population aged 25 and over has been reported to be around 40% (WHO, 2017c). The availability of low-cost medication has significantly decreased the occurrence of hypertension to e.g. 18% in the USA (WHO, 2017c; WHO, 2017d). Hypertension is a major risk factor for coronary heart disease and ischemic as well as hemorrhagic stroke, being responsible for ~50% of deaths due to these diseases (WHO, 2013). In addition, blood pressure level as continuous variable has been shown to

Table 1b
Insulin resistance and diabetes mellitus in childhood cancer survivors.

Author	Year	N	Population	Design	Follow-up	% IR	% DM	MVA	Prognostic variable
Holmqvist†	2014	32903	CCS	3	10y Mdn (0-42y)	n.a.	1.5	Yes	Tumor types: WT, leukemia, CNS, germ-cell, bone, HL
Meacham†	2009	8599	CCS	2	23.5y M (16.0-35.2y)	n.a.	2.5	Yes	TBI, Abd RTx, alkylating agent, younger age at diagnosis; no association: CRT, corticosteroids, asparaginase
Baker†	2007	1089	SCT (adult)	2	8.6y M (± 5.1y)	n.a.	7.6	Yes	TBI
Hoffmeister†	2004	748	SCT	3	11y Mdn (2.0-30.0y)	n.a.	4.5	Yes	CML, AML, ALL, asparaginase toxicity
Chao†	2016	652	CCS	2	6.2y M (± 4.1y)	n.a.	1.1	Yes	n.a.
Neville†	2006	248	CCS	1	12.9y Mdn (2.3-33.6y)	6.9 (IGT)	9.7	Yes	TBI, hypogonadism
Latoch†	2016	75	CCS	2	11.8y M (± 5.2y)	1.33 (HOMA-IR)	n.a.	Yes	n.a.
Moustoufi	2016	14290	CCS	2	24y Mdn (5-39y)	n.a.	0.5-3.8	No	CRT > 18 Gy, TBI, Abd RTx (among survivors)
Kero	2016	2530	CCS	3	10.4y Mdn (0-18y)	n.a.	3.5	No	ALL, AML, CNS
De Vathaire	2012	2520	CCS	3	n.a.	n.a.	2.6	No	Pancreatic tail radiation
Van Waas	2013	532	CCS	3	17.9y Mdn (5.0-48.8y)	n.a.	0.9	No	WT, Abd RTx
Felicetti	2015	330	CCS	2	16.1y Mdn (5.1-33.0y)	n.a.	1.5	No	n.a.
Wilhelmsson	2014	204	SCT	3	12y Mdn (4-28y)	n.a.	9	No	n.a.
Shalitin	2014	139	Non-brain solid	3	9y Mdn (1.2-29.5y)	1.4 (IGT)	n.a.	No	n.a.
Gunn	2016	62	CCS	3	18.0y M (6.8-37.9y)	32.3 (HOMA-IR)	n.a.	No	n.a.
Wei	2016	35	ALL/AML SCT +	2	12.5y Mdn (3.2-18.2y)	34.2 (IGT)	17.1	No	n.a.
Cohen	2014	24	HR NBL SCT +	3	6.1y Mdn (1.0-15.2y)	45.8 (HbA1c)	4.2	No	n.a.

† Highest quality evidence, based on MVA (multivariable analysis), patient number and design (1 = prospective, 2 = cross-sectional, 3 = retrospective).
%IR: percentage of survivors with insulin resistance, defined by IGT (impaired glucose tolerance), HOMA-IR (homeostatic model assessment) or HbA1c level; CCS = childhood cancer survivors; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; SCT = hematopoietic stem cell transplantation; HR NBL = high-risk neuroblastoma; Mdn = median; M = mean; WT = Wilms tumor/nephroblastoma; CNS = central nervous system; HL = Hodgkin lymphoma; TBI = total body irradiation; Abd RTx = abdominal radiotherapy; CRT = cranial radiotherapy; CML = chronic myeloid leukemia; n.a. = not available.

be related to the risk of stroke, coronary heart disease, heart failure, peripheral vascular disease, renal impairment and retinal hemorrhage (Levy et al., 1996; Thrift et al., 1996; Staessen et al., 1997; Coresh et al., 2001; Emdin et al., 2015).

Already in 1989, Kantor described hypertension in 20% of long-term survivors of childhood renal cancer (Kantor et al., 1989). According to a Cochrane review by Knijnenburg, prevalence of hypertension in childhood cancer survivors ranges from 0% to 18.2% (Knijnenburg et al., 2013). Three reports thereafter showed even higher prevalence, and one of these observed a sharp increase with age, exceeding 70% by age 50 (Gunn et al., 2016; Dekkers et al., 2013; Gibson et al., 2017) (Table 1d). In most case control studies, survivors reveal relatively high hypertension rates (Armstrong et al., 2013; van Laar et al., 2014; Kero et al., 2016b; Gibson et al., 2017). A study in ~650 survivors found no significant difference between survivors and controls, but this was a study with a rather short follow-up time of 6 years (Chao et al., 2016). In the CCSS, the presence of hypertension significantly increased the risk of major cardiac events and cardiac-specific mortality (Armstrong et al., 2013). The aforementioned Cochrane review included 24 studies with ~4000 survivors in total, and a high BMI was the only consistent independent risk factor for hypertension reported in multiple studies (Cardous-Ubbink et al., 2010; Hoffmeister et al., 2010). Other reported independent risk factors are the use of total body or abdominal irradiation, nephrectomy, acute kidney injury, SCT, growth hormone therapy, older age at screening and male sex (Gunn et al., 2016; Knijnenburg et al., 2013; Gibson et al., 2017).

Hypertension in CCS may be caused by direct kidney damage through irradiation (Breitz, 2004). Unilateral nephrectomy is known to induce hyperfiltration in the remaining kidney, which may give rise to hypertension (Schell et al., 1995). Ifosfamide and cisplatin have nephrotoxic side effects (Dekkers et al., 2013; Oberlin et al., 2009; Skinner et al., 2009), but hypertension is not reported as a consequence of these agents; one study reported a non-significant risk increase (Cardous-Ubbink et al., 2010). In the general adult population, it is known that treatment of hypertension towards below 140/90 mmHg is associated with a reduction in cardiovascular complications (Blood Pressure Lowering Treatment Trialists et al., 2008). This suggests that identification and treatment of subclinical hypertension in childhood cancer survivors by standard surveillance may decrease morbidity and mortality (Dekkers et al., 2013; Gibson et al., 2017).

4. The metabolic syndrome in childhood cancer survivors

4.1. Definition

Metabolic syndrome is a cluster of adiposity, IR/DM, dyslipidemia and hypertension (NCEP-ATP III, 2002; Alberti et al., 2006; Alberti and Zimmet, 1998). It was first described by Reaven in 1988, who found a clustering of symptoms in patients and called this Syndrome X (Reaven, 1988). The symptoms of this cluster are related and interacting in various ways. In general, imbalance in energy intake and consumption results in increased (visceral) adiposity. Secondary effects of adiposity include increased circulating FFA and reduced adiponectin – thus, an increase in IR factors – and increased pro-inflammatory and pro-thrombotic mediators such as IL-6, TNF-alpha and PAI-1. Increased lipid flux into the liver can result in steatosis, which also mediates IR. The liver also produces fibrinogen, enhancing the pro-thrombotic state. IR in liver and muscle leads to hyperinsulinemia, with a result of adipose tissue growth and tissue resistance to insulin. Hyperinsulinemia also contributes to hypertension through enhanced sodium resorption and sympathetic nervous system activation (Moller and Kaufman, 2005; Eckel et al., 2005). It is estimated that 20–25% of the world's adult population suffers from MetS (Alberti et al., 2006) and, consequently, are three times more likely to have a heart attack or stroke and twice as likely to die from cardio- and cerebrovascular disease, compared to people without MetS. In addition, patients with MetS are five times

Table 1c
Dyslipidemia in childhood cancer survivors.

Author	Year	N	Population	Design	Follow-up	% Dyslipidemia	MVA	Prognostic variable
Chao†	2016	652	CCS	2	6.2y M (± 4.1y)	1.8	Yes	n.a.
Felicetti†	2015	330	CCS	2	16.1y Mdn (5.1-33.0y)	20% (↑chol.), 6% (↑trigl.)	Yes	↑chol.: older age at diagnosis, TBI, GHD, auto-SCT; ↑trigl.: TBI, GHD
Armstrong	2013	10724	CCS	3	25.6y Mdn (7.4-39.3y)	8.9	No	n.a.
Kero	2016	2530	CCS	3	10.4y Mdn (0-18y)	2.2	No	n.a.
Brouwer	2013	277	CCS	2	18y Mdn (5-31y)	33 (↑chol.)	No	n.a.
Wilhelmsson	2014	204	SCT	3	12y Mdn (4-28y)	7	No	n.a.
Staba	2013	168	CCS	2	11.4y M (± 6.3y)	16	No	n.a.
Shalitin	2014	139	Non-brain solid	3	9y Mdn (1.2-29.5y)	10.9	No	n.a.
Morel	2017	80	ALL	2	12.4y M (± 0.71)	50	No	n.a.
Gunn	2016	72	CCS	3	18.0y M (6.8-37.9y)	50	No	n.a.
Wei	2016	35	ALL/AML SCT+	2	12.5y Mdn (3.2-18.2y)	62.9 (↑trigl.), 34.3 (↓HDL)	No	n.a.

† Highest quality evidence, based on design (2 = cross-sectional, 3 = retrospective) and MVA (multivariable analysis). CCS = childhood cancer survivors; (auto-) SCT = (autologous) hematopoietic stem cell transplantation; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; M = mean; Mdn = median; ↑chol. = hypercholesterolemia; ↑trigl. = hypertriglyceridemia; ↓HDL = low high-density lipoprotein; TBI = total body irradiation; GHD = growth hormone deficiency; n.a. = not available.

more likely to develop DM2 and people with diabetes are three times more likely to develop cardiovascular disease (Alberti et al., 2006; Wilson et al., 2005; Ford, 2004) (Fig. 1). Metabolic syndrome is also associated with fatty liver disease, gallstones, hepatocellular carcinoma, chronic kidney disease and polycystic ovary syndrome (Marceau et al., 1999; Hamaguchi et al., 2005; Chen et al., 2004; Kurella et al., 2005; Pasquali et al., 1999; Siegel and Zhu, 2009; Akanji and Smith, 2012).

Currently, three definitions of metabolic syndrome are commonly used: those created by the World Health organization (WHO) (Alberti and Zimmet, 1998), National Cholesterol Education Program – Third Adult Treatment Panel (NCEP/ATPIII) (NCEP-ATP III, 2002) and the International Diabetes Foundation (IDF) (Alberti et al., 2006) (Supplemental Table 2). Although the definition of MetS is based on the principle of clustered components, these components themselves are also independent risk factors for the development of cardiovascular disease (Moller and Kaufman, 2005). The prevalence of MetS can vary, depending on which definition is used. In young adults, who less frequently meet all MetS criteria, partial clustering of risk factors should be examined. The MetS definitions provide useful guidelines to identify those individuals at risk for development of DM2, atherosclerotic cardiovascular disease, and cardiovascular death. MetS is a “disguised” syndrome; without measurement of blood pressure and lipids, metabolic sequelae can develop for years. This underlines the need for active surveillance.

4.2. Risk and determinants

Several studies have focused on the development of MetS in CCS. Comparison of these studies is hampered by the fact that often small patient groups are analyzed, the heterogeneity of malignancies as well as therapies and the different definitions of MetS that are used. An overview of existing literature on the frequency of MetS and prognostic factors in CCS is presented in Table 2. The first study on this subject was by Talvensaari, reporting a prevalence of 16% in 50 survivors, compared to none of the controls (Talvensaari et al., 1996). Since then, reported frequencies of MetS in CCS vary between zero and 39 percent (van Waas et al., 2010; van Waas et al., 2012; Prasad et al., 2015; Talvensaari et al., 1996; Saultier et al., 2016; Oudin et al., 2015; Oudin et al., 2011; Nottage et al., 2014; Chow et al., 2010; Bizzarri et al., 2015; Blijdorp et al., 2013; Smith et al., 2014; Trimis et al., 2007; Mohapatra et al., 2016; Gurney et al., 2006; Aldhafiri et al., 2012; Karakurt et al., 2012; Hoffman et al., 2008; Taskinen et al., 2007; van Waas et al., 2013a; Ness et al., 2005; Kojima et al., 2013).

Our literature search retrieved twenty-two studies, six of which performed multivariable analyses in search of risk factors for developing MetS. Only three out of six had a prospective study-design. These were all reports from the French LEA program, a cohort of acute leukemia survivors (Saultier et al., 2016; Oudin et al., 2015; Oudin et al., 2011). MetS occurred in 6.9–17.1% of the survivors. In the first study, HSCT with TBI as conditioning regimen was the only risk factor for metabolic syndrome (OR 3.9). In the second study, TBI was not a risk factor for MetS, nor were gender, total post-transplant steroid dose and follow-up duration. The only risk factor was higher BMI at time of transplantation (OR 1.57). In the third study, male sex (OR 2.64), older age at evaluation and higher BMI at diagnosis were risk factors for MetS, whereas CNS irradiation was not. The three other studies with multivariable analyses had a cross-sectional or retrospective study design. The largest study investigated MetS in 784 ALL survivors in the St. Jude Lifetime Cohort, compared to 777 healthy controls (Nottage et al., 2014). Metabolic syndrome was present in 33.6 percent of survivors (RR 1.43). Risk factors in multivariable analyses were CRT, especially with craniospinal radiation (RR 1.88), and older age at evaluation. Steroid dose was not a risk factor. A smaller study in 74 ALL survivors also revealed HSCT (OR 22.99) as risk factor for MetS (Chow et al., 2010). In a large, retrospective study in 648 Indian childhood cancer survivors, no patient fully met all the criteria for MetS (Prasad et al., 2015). Only when overweight patients were included (next to obese patients), prevalence was 2.4% for underage (< 18 years old) survivors and 9.6% for survivors aged 18 years and older. It should be mentioned that follow-up in this study was short (6 and 11.5 years median for survivors below and over 18 years, respectively).

Of the remaining sixteen studies that our search yielded, three had a prospective design. The largest described MetS in a single center cohort of 103 nephro- and neuroblastoma survivors (van Waas et al., 2012). Survivors had more components of MetS than healthy controls (OR 5.2 in nephroblastoma, 6.5 in neuroblastoma) and frequency was three times higher in patients who received abdominal irradiation (28% vs 9%). A small study in 21 AML survivors reported SCT as risk factor for having more MetS components than healthy controls (OR 24.1), whereas chemotherapy only was not a risk factor (Blijdorp et al., 2013). In the third study, none of the 45 survivors of a hematological malignancy treated with HSCT had MetS (Bizzarri et al., 2015), but this was also a study with a short follow-up time. Risk factors described in the other studies include cranial (van Waas et al., 2010; Trimis et al., 2007; van Waas et al., 2013a) and abdominal radiation (van Waas et al., 2013a), while the other studies found no significant prognostic variables or did not perform this analysis.

Summarizing the studies with the highest quality of data, the following prognostic variables were risk factors for developing the MetS in

Table 1d
Hypertension in childhood cancer survivors.

Author	Year	N	Population	Design	Follow-up	% Hypertension	MVA	Prognostic variable
Knijnenburg†	2013	4073	CCS	1	Various	0-18.2	Yes	Higher BMI, TBI, Abd RTx, acute kidney injury, SCT, growth hormone therapy, older age at screening, male
Gibson†	2017	3016	CCS	2	> 10y	22.4	Yes	Older age, nephrectomy
Baker†	2007	1089	SCT (adult)	2	8.6y M (± 5.1y)	18.5	Yes	Allo-SCT
Chao†	2016	652	CCS	2	6.2y M (± 4.1y)	1.5	Yes	n.a.
Gunn†	2016	269	CCS	3	n.a.	19.0	Yes	Male, older age, overweight/obesity
Armstrong	2013	10724	CCS	3	25.6y Mdn (7.4-39.3y)	14.9	No	n.a.
Van Laar	2014	3247	CCS	3	> 5y	7.8/10.000py	No	n.a.
Kero	2016	2530	CCS	3	10.4y Mdn (0-18y)	12	No	ALL, bone tumor
Dekkers	2013	763	CCS	2	18.3y Mdn (5.0-58.2)	23.4	No	Renal tumor, Abd RTx
Essig	2014	556	ALL	3	18.4y Mdn (0.0-33.0)	13	No	n.a.
Felicetti	2015	330	CCS	2	16.1y Mdn (5.1-33.0y)	5.3	No	n.a.
Brouwer	2013	277	CCS	2	18y Mdn (5-31y)	14	No	n.a.
Wilhelmsson	2014	204	SCT	3	12y Mdn (4-28y)	7	No	n.a.
Shalitin	2014	139	Non-brain solid	3	9y Mdn (1.2-29.5y)	8.6	No	n.a.
Interiano	2015	75	WT	2	19.6y Mdn (10.0-32.8)	6.7	No	n.a.
Wei	2016	35	ALL/AML SCT+	2	12.5y Mdn (3.2-18.2y)	17	No	n.a.

† Highest quality evidence, based on design (1 = Cochrane review, 2 = cross-sectional, 3 = retrospective) and MVA (multivariable analysis).
CCS = childhood cancer survivors; (allo-)SCT = (allogeneic) hematopoietic stem cell transplantation; WT = Wilms tumor/nephroblastoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; M = mean; Mdn = median; py = person years; TBI = total body irradiation; Abd RTx = abdominal radiotherapy; n.a. = not available.

CCS: the treatment components HSCT, CRT, TBI (although not all studies support this finding) and abdominal radiation, and the patient characteristics male sex (not in all studies), higher BMI at diagnosis or time of transplantation, and older age at evaluation.

5. Pathophysiology of the metabolic syndrome in childhood cancer survivors

5.1. Growth hormone deficiency

Disease as well as treatment, i.e., respectively, brain tumors, CRT (Huma et al., 1995; Darzy and Shalet, 2003; Chemaitilly et al., 2015; Davis et al., 2015; Follin et al., 2016) and brain surgery (Thomsett et al., 1980; Stahnke et al., 1984), but also TBI (Huma et al., 1995; Davis et al., 2015; Felicetti et al., 2011) and chemotherapy (Gleeson et al., 2004; Haddy et al., 2006) can damage the hypothalamus and pituitary gland, which leads to several endocrine disorders, the most common being GHD (Darzy and Shalet, 2003; Rose et al., 2016; Chemaitilly and Cohen, 2017). GHD induces the components of the metabolic syndrome, as shown in several studies: adiposity (de Boer et al., 1992; Binnerts et al., 1992; Rosén et al., 1993; Franco et al., 2006), insulin resistance (Hew et al., 1996; Johansson et al., 1995), dyslipidemia (Rosén et al., 1993; de Boer et al., 1994; Bengtsson et al., 1999) and hypertension (Rosén et al., 1993; Bengtsson et al., 1999; Friedman et al., 2017). A recent study in CCS associated GHD with the development of clusters of three or more cardiovascular risk factors (Friedman et al., 2017). GHD has also been linked to endothelial dysfunction and atherosclerosis (Elhadd et al., 2001; Cannavo et al., 2011) and to decreased left ventricular ejection fraction (Colao et al., 2004), further increasing the risk of cardiovascular complications. Schneider et al. reported an increased ten-year risk of cardiovascular events in ~350 GHD patients compared to healthy controls (4.6% vs. 3.7%) (Schneider et al., 2011).

The hypothalamus, rather than the pituitary gland, is regarded as the primary site of radiation damage (Darzy and Shalet, 2003; Crowne et al., 2015; Follin and Erfurth, 2016). The somatotropic axis is affected first, followed by the gonadal axis, and, least sensitive, the thyroid and adrenal axis (Darzy and Shalet, 2003; Chemaitilly et al., 2015; Darzy and Shalet, 2009). After radiotherapy growth hormone secretion may gradually and irreversibly decrease over the course of years in a dose-dependent manner; at 16 Gy the risk of developing GHD five year off treatment is 50% (Merchant et al., 2011). The most relevant radiotherapy threshold is not clear: other reported thresholds are 18 Gy (Mostoufi-Moab et al., 2016), 22 Gy (Chemaitilly et al., 2015) and 30 Gy (Darzy and Shalet, 2009). In a meta-analysis by Mulder the pooled prevalence of GHD after cranial radiation was 35.6% (Mulder et al., 2009).

In non-cancer survivors with GHD, it has been shown that growth hormone replacement has positive effects on cardiac function, cardiovascular risk factors such as body composition, lipid levels and blood pressure, and on the occurrence of cardiovascular events (Schneider et al., 2011; Baum et al., 1996; Bengtsson et al., 1993; Maison and Chanson, 2003; Maison et al., 2004; van Bunderen et al., 2014). On the other hand, a large study in ~2500 growth hormone deficient adults found no decrease in the prevalence of MetS after three years of replacement (Attanasio et al., 2010), and Claessen even reported a substantial increase in MetS after ten years of treatment in 98 patients, from 32.7% to 57.1% (Claessen et al., 2013). Unfortunately, there is only scarce literature on growth hormone replacement in CCS. Furthermore, clinical interpretation of these studies is commonly complicated by methodologic shortcomings such as lack of a control group and the use of surrogate markers instead of cardiovascular morbidity and mortality. A small study in eighteen ALL survivors with GHD on two years' replacement therapy reported improved cardiac systolic function and reduced incidence of metabolic syndrome (Follin et al., 2006). Another small study with eleven ALL survivors on twelve months'

Table 2
Metabolic syndrome in childhood cancer survivors.

Author	Year	N	Population	Design	Follow-up	MetS definition	% MetS	MVA	Prognostic variable	**Control group**
Saultier†	2016	650	ALL/AML SCT-	1	16y M (± 6.79y)	NCEP ATP III	6.9	Yes	Male, older age and high BMI at diagnosis	n.a.
Oudin†	2011	184	ALL/AML	1	15.4y Mdn (3.4-30.2y)	NCEP ATP III	9.2	Yes	TBI-SCT	n.a.
Oudin†	2015	170	ALL/AML SCT+	1	14.5y M (± 6.1y)	NCEP ATP III	17.1	Yes	High BMI at transplantation	n.a.
Nottage†	2014	784	ALL	2	26.1y Mdn (11-45.3y)	NCEP ATP III	33.6 (RR 1.43)	Yes	CRT	777 Healthy NHANES
Chow†	2010	74	ALL	2	10y/10.5y Mdn (1-18y)	IDF	10.8	Yes	TBI-SCT, CRT, positive family history	n.a.
Prasad	2015	648 (471 < 18y)	CCS	3	6y Mdn (2-16y) (< 18y); 11.5y Mdn (2-41y) (≥18y)	IDF	0	Yes	n.a.	n.a.
Van Waas	2012	103	WT/NBL	1	26.2y Mdn (6.4-48.9y)	NCEP ATP III	14 (WT) / 6 (NBL)	No	Abd RTx	61 HC
Bizzarri	2015	45	Hemat. malig. HSCT+	1	4y M (± 3.2y, NGT)/6.9y M (± 3.1y, IGT)	(modified) NCEP ATP III	0 (NS)	No	n.a.	90 HC
Blijdorp	2013	21	AML ± SCT	1	20y Mdn (9-31y)	NCEP ATP III	8.3 (SCT-), 12.5 (SCT+, OR 24.1)	No	SCT	48 HC
Smith	2014	1598	CCS	2	25.6y M (± 7.6y)	NCEP ATP III	31.8	No	n.a.	n.a.
Van Waas	2010	500	CCS	2	19y Mdn (6-49y)	Modified NCEP ATP III	13	No	CRT, ALL, male	n.a.
Trimis	2007	80	ALL	2	6.37 Mdn/5.9y M (1.1-12.2y)	Modified NCEP ATP III / WHO	11	No	CRT	n.a.
Mohapatra	2016	76	ALL	2	3y Mdn (IQR 2.3-5y)	IDF / NCEP ATP III	1.3 (IDF) / 5.2 (NCEP ATP III)	No	n.a.	n.a.
Gurney	2006	75	ALL	2	24.6y M (± 4.8y)	NCEP ATP III	16.6	No	n.a.	730 Healthy NHANES
Aldhafiri	2012	56	ALL	2	6.2y M (± 3.9y)	IDF / NCEP ATP III	7.1 (IDF) / 5.4 (NCEP ATP III)	No	n.a.	n.a.
Talvensaari	1996	50	CCS	2	12.6y M (7.9-21.3y)	Obesity, ↑insulin, ↓HDL	16	No	n.a.	50 HC
Karakurt	2013	44	ALL	2	5.4y M (3-10y)	IDF	6.8	No	n.a.	119 Family members
Hoffman	2008	32	Sarcoma	2	17.3y Mdn (2.9-32.6y)	NCEP ATP III	33 (OR 4.29 20-39y)	No	n.a.	U.S. population data
Taskinen	2007	31	SCT	2	6y Mdn (1-20y)	WHO	39	No	n.a.	n.a.
Van Waas	2013	532	CCS	3	17.9y Mdn (5.0-48.8y)	Modified NCEP ATP III	15	No	CRT, Abd RTx	n.a.
Ness	2005	486	Adult CS	3	n.a.	NCEP ATP III	25.8	No	Breast cancer history	12,526 HC
Kojima	2013	49	CCS	3	5.1y Mdn (3.0-14.6y)	Japanese criteria	6.1	No	n.a.	n.a.

† Highest quality evidence in bold, based on design (1 = prospective, 2 = cross-sectional, 3 = retrospective) and MVA (multivariable analysis).
%MetS: percentage of survivors with MetS, with RR (relative risk) or OR (odds ratio) when statistically significant compared to control group; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; SCT = hematopoietic stem cell transplantation; CCS = childhood cancer survivors; WT = Wilms tumor/nephroblastoma; NBL = neuroblastoma; M = mean; Mdn = median; NGT = non-impaired glucose tolerance; IGT = impaired glucose tolerance; IQR = interquartile range; HDL = high-density lipoprotein; NCEP ATP III = National Cholesterol Education Program – Third Adult Treatment Panel; IDF = International Diabetes Foundation; WHO = World Health Organization; CRT = cranial radiotherapy; TBI = total body irradiation; Abd RTx = abdominal radiotherapy; NHANES = National Health And Nutrition Examination Survey; HC = healthy controls; n.a. = not available.

growth hormone replacement reported positive effects on fat mass and fat free mass, but hyperleptinemia and insulin resistance remained unaffected (Bulow et al., 2004). Van den Heijkant found higher lean mass and lower percentage fat after two years of therapy in 14 ALL survivors (van den Heijkant et al., 2011), and Murray reported beneficial effects on waist-hip ratio, cholesterol and triglycerides in 27 ALL and brain tumor survivors after twelve months' therapy (Murray et al., 2002).

5.2. Gonadal impairment, thyroid morbidity and adrenal insufficiency

The production of other pituitary hormones, and damage to other endocrine end organs seems to be less frequently affected after childhood cancer and therapies. CRT > 30 Gy caused long-term central hypogonadism in 20–30% of survivors (Darzy and Shalet, 2009), and regimens harming the gonads can be causative factors as well (Nord et al., 2003; Wallace et al., 2005; Huddart et al., 2005; Sprauten et al., 2014). Mainly tested in men, hypogonadism is reported to contribute to MetS and vice versa (Zitzmann, 2009; Brand et al., 2011; Akinloye et al., 2014; Naifar et al., 2015; Ventimiglia et al., 2016). A few studies associated gonadal impairment with MetS traits in CCS (Neville et al., 2006; Hoffman et al., 2008; van Dorp et al., 2013; Blijdorp et al., 2014; Jahnukainen et al., 2015). A recent meta-analysis reported that testosterone supplementation in men with testosterone deficiency syndrome had positive effects on body weight and composition and glucose and lipid metabolism (Corona et al., 2016). There are no studies available that investigated the effect of sex hormone therapy on the metabolic syndrome in CCS, so far.

Cranial radiation doses of 30 Gy and higher caused central hypothyroidism in 3–9% of survivors (Darzy and Shalet, 2009). Thyroid malignancies (although rare in children) or neck and mantle radiation for other cancer types damage the thyroid and lead to primary hypothyroidism (Jereczek-Fossa et al., 2004; Hancock et al., 1995). Metabolic manifestations of hypothyroidism include adiposity, hypertension (due to an increase in peripheral vascular resistance) and dyslipidemia (Taddei et al., 2003; Duntas and Brenta, 2012; Knudsen et al., 2005; Waring et al., 2012). As in the normal population, hypothyroidism after childhood cancer is treated with levothyroxine. Although it is anticipated that levothyroxine treatment has positive effects on the metabolic profile of CCS, no studies have investigated this yet.

Adrenal insufficiency occurred in 3–6% of patients receiving > 30 Gy CRT (Darzy and Shalet, 2009) and can also temporally be caused by high-dose steroid treatment. Hypocortisolism in itself is not associated with MetS features, but treatment with corticosteroids – especially dexamethasone – is notorious for causing short term adiposity, IR and diabetes (Gurwitz et al., 1994; Da Silva et al., 2006). It is conceivable that the use of glucocorticoids in childhood cancer treatment can have these consequences on long term as well. Van Beek showed that treatment with prednisone or dexamethasone is associated with long term increases in BMI and body fat in ALL and Hodgkin lymphoma survivors (van Beek et al., 2006; van Beek et al., 2009).

5.3. General fitness

Another potential mechanism for the development of MetS in CCS is physical inactivity, as this promotes obesity and IR. In the St. Jude Lifetime cohort, 28% of survivors were found not to adhere to lifestyle guidelines. Males and females who did not follow these guidelines were approximately twice more likely to have MetS (Smith et al., 2014). Similarly, Warner reported total energy expenditure and physical activity to be lower in 34 ALL survivors compared to 21 survivors of other childhood malignancies, and to healthy controls. This was negatively associated with percentage body fat, but it remains the question whether this is either a cause or a consequence (Warner et al., 1998). Additionally, we showed that especially male neuroblastoma survivors might be at risk for reduced physical activity (van Waas et al., 2013b). Visual impairment after certain brain tumors may enhance MetS risk, due to the reduced ability to perform physical activity. For example, in a study in 178 childhood- and adult-onset craniopharyngioma survivors, visual impairment was a borderline significant independent risk factor for MetS (Wijnen et al., 2018). To date, it is not entirely clear yet whether reduced physical activity and sedentary lifestyle play a causative role in development of MetS. However, as it is one of the few modifiable factors that might decrease MetS, it is of great value to initiate intervention studies with regard to physical activity in CCS.

5.4. Genetic susceptibility

The role of genetic susceptibility in the development of MetS and cardiovascular disease in childhood cancer survivors has not been extensively studied yet. In our cohort of 532 survivors, we used a candidate gene approach, containing genes previously associated with components of the metabolic syndrome, i.e. JAZF1, THADA, IRS1, TFAP2B, MSRA and ATP2B1 (van Waas et al., 2013a). None of the allelic variants was associated with metabolic syndrome, indicating that treatment factors were more dominant than genetic variation. England et al. performed whole-exome sequencing in 209 ALL survivors and reported that variants in BAD and FCRL3 genes were associated with a phenotype of three or more cardiometabolic risk factors (England et al., 2017). In the St. Jude Lifetime cohort, a genome-wide association study (GWAS) identified single nucleotide polymorphisms associated with obesity in the following genes: FAM155 A, which is expressed in the hypothalamus and pituitary, and GLRA3, SOX11 and CDH18, which are involved in neural growth, repair and connectivity (Wilson et al., 2015). To date, these findings have not been validated, nor has GWAS been performed to identify genetic variants associated with diabetes, dyslipidemia, hypertension and MetS in CCS (Clemens et al., 2018).

6. Summary and future perspective

After almost 25 years of research on childhood cancer survivors, we have gained knowledge on potential late effects, of which the metabolic syndrome so far has been rather disguised. Many CCS are already at risk for cardiovascular disease, for example, due to anthracycline- or radiation-induced cardiotoxicity (Kremer et al., 2002; van Dalen et al., 2006; van der Pal et al., 2012). Additionally, they face an additive risk after CRT, causing GHD and MetS. The role between MetS and other risk factors, such as abdominal radiation, specific chemotherapeutic agents, steroids, gonadal impairment, thyroid morbidity and genetics, warrants further investigation. It is however clear that specific groups of CCS are at higher risk of developing components of the MetS (Fig. 1), which underlines the need for close monitoring. These survivors might benefit from early interventions targeting overweight, hypertension and dyslipidemia, for instance lifestyle and diet advice and medication (Moller and Kaufman, 2005). Since MetS is a cluster of symptoms with heterogeneous presentation among individuals, medical treatment requires a personalized approach (Moller and Kaufman, 2005).

In our opinion, future research may focus on the following three topics: 1) Unravelling the pathophysiologic mechanism of the development of the MetS in specific CCS subgroups, 2) Determining which subgroups of CCS are at risk to develop (components of) MetS by using prediction models, and 3) Determining which preventive and therapeutic interventions are successful in targeting the MetS in CCS – favourably multiple components with the same intervention. As childhood cancer is relatively rare, research will benefit from collaborations between (inter)national cohorts, to enhance effect size and for replication purposes.

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Declarations of interest

None

Conflicts of interest

The authors have no conflicts of interest to declare with regard to this publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2018.10.010.

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