Nutritional status in children with cancer

Prevalence, related factors, and consequences of malnutrition

“

“Doordat ik eerst veel sportte en daarna lang stil lag in bed, verdwenen mijn spieren, viel ik af en moest ik de kilo’s erbij eten in vet. Deze moeten er nu weer af en dat kost mij veel energie.”

meisje, 15 jaar

“Ze wil bijna niets eten. Ze kan de geur van eten niet verdragen. Ze krijgt sondevoeding, maar ook die geur kan ze niet verdragen. Als ze alleen een hapje spaghetti eet, zijn we al blij. Alle kleine beetjes eten helpen.”

moeder van 3-jarig meisje

“Soms heb ik ergens zin in maar dan smaakt het heel anders. En nu lust ik geen bananen meer.“

meisje, 5 jaar

“Ik ben bijna 20 kilo aangekomen, maar in vergelijking met mijn ziekte is het helemaal niet zo erg dat ik een paar kilo zwaarder ben.”

jongen, 16 jaar

“Ik ben nooit verdrietig, ik ben altijd vrolijk.”

jongen, 5 jr

“Ik vind het prima dat hij wat zwaarder is. In het begin is hij erg afgevallen en ik vind het wel fijn dat hij nu wat reserve heeft. Hij heeft nog veel kuren te gaan”.

moeder van 8-jarige jongen

"Zo op het oog lijkt het goed te gaan met hem, maar vorige week was hij helemaal in tranen. Mijn zoon vertelde dat hij bij gym niet meer als één van de eersten gekozen werd, terwijl dat eerder altijd wel het geval was. En op school mag hij niet meer de extra stof doen, maar moet hij meedoen met de reguliere lesstof. Hij moet dus wel degelijk "inleveren" op gewone dingen."
vader van 10-jarige jongen

"Ik was 2x bijna dood geweest, dat hadden papa en mama mij verteld. Gelukkig ging ik niet dood want nu kan ik mijn papa weer plagen."
meisje, 6 jaar

"Ik wil graag samen met mijn zoon de lijsten invullen. Er komen vragen aan bod waar je het anders niet over hebt en waar hij soms een hele andere mening over heeft dan wij. Dat is leuk om te horen vooral omdat hij veel positiever over veel dingen denkt".
moeder van 8-jarige jongen

"Ze is na de behandeling enorm gaan eten, ze wil steeds eten en is daardoor dik geworden. Ze is een stress eter net als ik. Nu let ik erop dat er geen grammetje meer bijkomt. Als ze iets gegroeid is, mag ze de volgende dag niet snoepen."
moeder van 6-jarig meisje

"Ik kan niet meer goed nadenken, mijn hoofd is helemaal leeg".
meisje, 15 jaar

"Ze vindt haar haar nog steeds niet lang genoeg al zegt de hele wereld anders."
vader van 9-jarig meisje

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Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

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Prof. dr. R. Sanderman
Prof. dr. E.S.J.M. de Bont

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Beoordelingscommissie
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Prof. dr. M.J. Schuurmans
Prof. dr. A.A.E. Verhagen

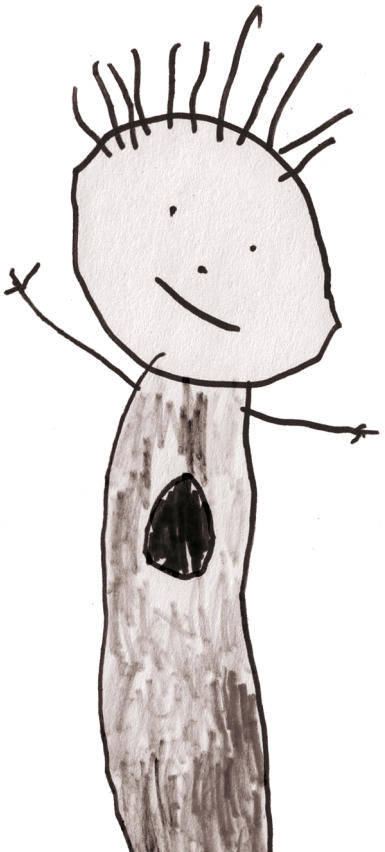
"Nutrition should be viewed for what it is: supplying the most basic needs of children. No child has died for being fed appropriately, but many die of starvation. The practice of pediatric oncology should not contribute to that statistic."

Jan Van Eys 1986, Cancer

CONTENTS

CHAPTER 1

INTRODUCTION



AIM OF THE THESIS

The general aim of this thesis is to evaluate the nutritional status in children with cancer during the first year after diagnosis. The more specific aims are:

- to determine the prevalence of malnutrition;
- to determine the onset of malnutrition and the course of the nutritional status;
- to explore which factors contribute to changes in nutritional status;
- to determine the clinical implications of malnutrition with regard to survival and infection risk;
- to determine the impact of nutritional status on HRQOL.

1

INTRODUCTION

Although childhood cancer is a rare disease with an incidence rate of 14.3 per 100,000 children per year,[1] it is the most common cause of death in children in the Western World.[2,3] In the Netherlands, 550 children (0-18y) are diagnosed with cancer each year,[4] and about 120 of these children die because of the disease or because of the side effects of treatment.[1] This means that every 3 days a child dies because of cancer.

To date, knowledge about the causative factors of childhood cancer is still limited.[5] The different types of childhood cancer can be grouped into hematological, solid, and brain malignancies. Two of the most common types are leukemia and brain tumors, accounting for 25% and 21% of all cancer cases respectively (Figure 1).[4]

During the past few decades, treatment of childhood cancer has greatly improved. Early detection; enhanced treatment modalities combining chemotherapy, surgery, and radiation; and improvement in supportive care[6] have caused 5-year survival to increase from 28% in the late 1960s to about 80% in 2010.[1] This means that treatment of children with cancer is more successful than treatment of adult patients with cancer; recent statistics reported 61% survival in the latter group.[7] In general, childhood cancers respond better to chemotherapy because these cancers tend to be fast-growing and chemotherapy affects cells that grow quickly. Moreover, children are better able to physically recover from higher doses chemotherapy compared with adults.

The ambitions for the coming decades are (1) to improve survival rates, and in the end, to cure all children with cancer; and (2) to reduce short term and long term side effects of treatment in order to improve quality of life of childhood cancer patients and childhood cancer survivors. Therefore, in the coming years, therapy will be better tailored to patients based on the genotypes of their cancer. In addition, research on supportive care is necessary to develop interventions that reduce side effects such as infections, mucositis, and malnutrition and to make sure that children are physically and mentally in the best possible condition to cope with the intensive therapy. Reducing treatment-related morbidity will improve quality of life[8] both during and after treatment and will eventually have a positive effect on survival rates.

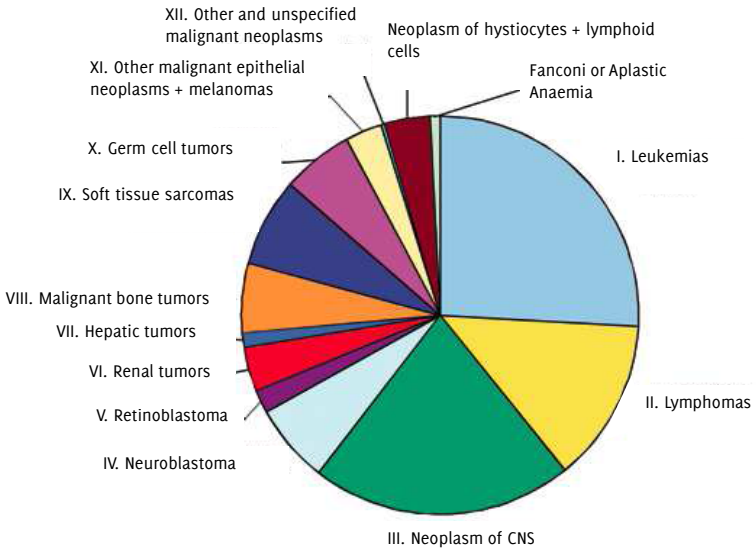


Figure 1. Incidence of childhood cancer in the Netherlands.[4]

NUTRITIONAL STATUS

The role of nutrition in the treatment of cancer has not always received the attention it deserves. In the 1970s, pediatrician Jan van Eys was the first to plead for recognition of malnutrition as an isolatable problem that could be treated in the same way as an infection.[9] Oncologists were often reluctant to provide nutritional support, fearing this would enhance tumor growth. Despite the fact that evidence for this assumption was lacking[10-12] and that the benefits of treating malnutrition have been demonstrated,[13] the relevance of nutritional status is still frequently ignored and its effects on the course of treatment are underestimated. To date, several studies have demonstrated the prognostic effect of nutritional status on outcomes of cancer therapy.[14,15] This point will be discussed into more detail in one of the following sections. First, the concepts of nutritional status and malnutrition will be discussed in more detail.

Definition nutritional status

Nutritional status can be defined as the state of the body in relation to the consumption and utilization of nutrients; it represents the extent to which

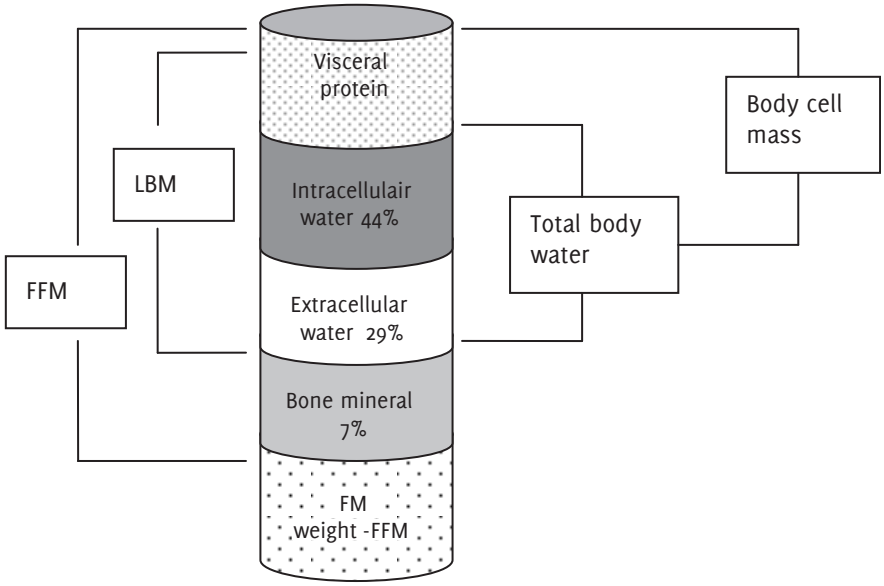


Figure 2. Body composition expressed in different components. FFM, fat free mass; LBM, lean body mass; FM, fat mass.

the dietary nutrients meet the physiologic needs of the body. Nutritional status can be represented by both body size and body composition. Body size is measured using weight and height and is expressed in weight-for-age (WFA), height-for-age (HFA), weight-for-height (WFH), and BMI-for-age. Body composition can be expressed in two components: fat mass (FM) and fat free mass (FFM); in three components: FM, lean body mass (LBM) and bone mass; or in multiple components in which LBM is divided into body cell mass and water (Figure 2).[16,17] FM, FFM, or LBM represent the nutritional stores of the body.[18]

Malnutrition is defined as a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form and function and clinical outcomes.[19] Although malnutrition is often used to refer to the undernourished state, it actually includes both undernutrition and overnutrition. In this thesis the term malnutrition therefore refers to both states of nutrition.

Several criteria are used to classify nutritional status. Nowadays, cut-off values are given in terms of standard deviation scores (SDS).[20,21] SDS represent the measured value minus the mean value in a population divided by the standard

deviation of that population. In order to define undernutrition, cut-offs have been proposed of <-2 SDS; whereas overnutrition is defined by cut-offs of >2 SDS.[20]

Prevalence of malnutrition

Undernutrition is frequently present in children with cancer. Reported prevalence rates range from 0 to 50%.[14,15] Prevalence rates depend on the type of tumor, the extent of the disease, the treatment modality, the standard of living, and the criteria used to define undernutrition.[2] The highest prevalence rates, ranging from 30% to 50%, are found in children with medulloblastoma[22] and neuroblastoma.[23,24] Overnutrition is particularly reported in children treated for leukemia[25] and in certain brain tumors.[26] Prevalence rates of up to 40% have been reported in these children.[27]

However, despite the impressive number of studies on malnutrition, a precise understanding of the prevalence of under- and overnutrition or of patients at risk is lacking. In addition, little is known about the timing and onset of under- and overnutrition and the changes in nutritional status over time. To date, most studies that have researched nutritional status relied on cross-sectional data. The few prospectively conducted longitudinal studies that did report on changes in nutritional status predominantly concerned patients with acute lymphoblastic leukemia (ALL)[28,29] or relied on small sample sizes.[30-32]

Remarkably, weight loss and decreased growth are seldom included in the assessment of nutritional status. Only a few studies have reported on weight loss, in particular in children with medulloblastoma.[22,35] Although growth is one of the most important features of children's health, little is known about the magnitude and severity of weight loss and decreased growth in children with cancer.

Related factors of malnutrition

In theory, the onset of and the factors contributing to under- or overnutrition are clear. Undernutrition and overnutrition are usually the consequence of energy imbalances.[36] Figure 3 presents a conceptual frame work of causes of undernutrition. It is hypothesized that weight loss and undernutrition in cancer patients are induced by energy deficiency and/or inflammation.[37] Energy deficiency may occur because energy intake is diminished, because energy requirement is increased, or because both are altered. Energy deficiency results in loss of fat mass and, to a lesser extent, in loss of fat free mass. Inflammation can alter protein, lipid, and carbohydrate metabolism,

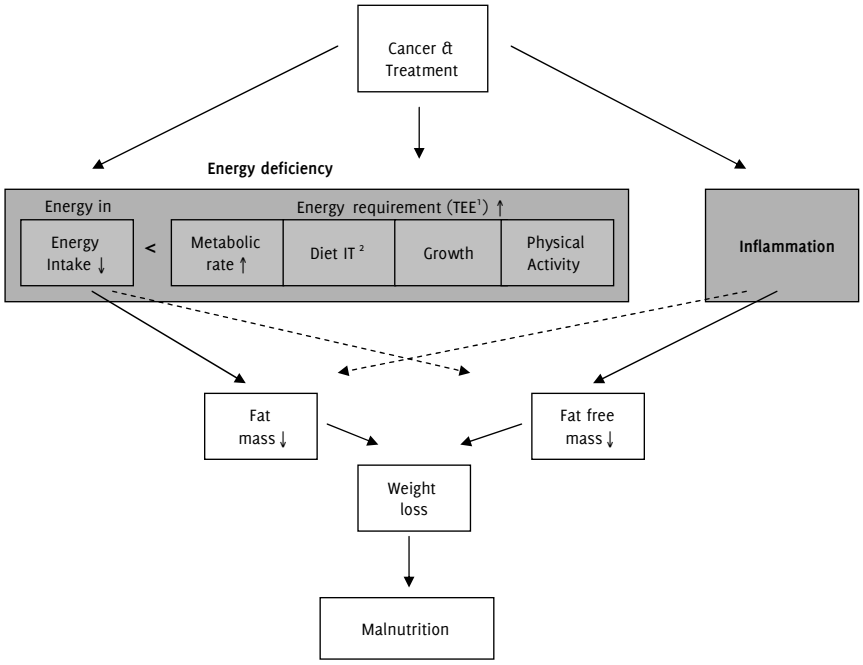


Figure 3. Conceptual model of determinants of undernutrition. This model was adapted from Evans 2008[37] and Soeters 2009.[40] [1]TEE= Total Energy Expenditure; [2]Diet IT= Diet Induced Thermogenesis.

which may also contribute to weight loss,[2,38,39] especially to loss of muscle mass.[40,41] Sometimes fat mass is lost as well.[42-44] This process is often described as cachexia.[37,45] Cachexia is a complex metabolic syndrome associated with cancer and characterized by weight loss or growth failure, anorexia, muscle wasting, decreased muscle strength, fatigue, and abnormal biochemical parameters (increased inflammatory markers, anemia, low serum albumin).[37] Cachexia is more difficult to treat than undernutrition induced by energy deficiency.

A similar framework could be presented for the causes of overnutrition. Increased energy intake and reduced physical activity are commonly considered to be responsible for weight gain and overnutrition.[25,46] In addition, weight gain is often attributed to corticosteroid therapy, which is known to promote alterations in fat metabolism and insulin sensitivity.[46,47] Moreover, children treated with cranial radiotherapy (CT) or brain surgery, the latter of which can damage the hypothalamic-pituitary axis, are at increased

risk of overnutrition among others because of growth hormone deficiency and leptin insensitivity.[48-50] However, even in children who were not treated with cranial radiotherapy, the prevalence of overnutrition is higher than in the general population.[25,48] This finding shows that not all mechanisms related to nutritional status are fully understood, making it difficult to pinpoint which factors contribute substantially to changes in nutritional status. Unambiguous evidence for causality is still lacking.

Consequences of malnutrition

In patients with ALL and acute myeloid leukemia (AML), both undernutrition and overnutrition are associated with lower survival rates.[51-54] Moreover, undernutrition has been associated with more complications such as infections, treatment delay, and higher relapse rates.[2,15,55] However, whether these associations hold true for children with other malignancies than leukemia is not known. Poor survival prospects have also been demonstrated in overnourished leukemia patients.[51,52] In addition, overnutrition is rapidly becoming a problem in survivors of childhood cancer. Prevalence rates as high as 25% to 50% have been reported in ALL survivors.[46] This is of major concern, given the cardiovascular, metabolic, psychosocial, and other late effects which survivors of childhood cancer face.[56] Obesity may contribute to these effects or even exacerbate them.[25]

To date, the majority of studies that have reported on consequences of nutritional status on morbidity and mortality only evaluated patients at diagnosis and only concerned patients with leukemia.[57] Thus, little is known about the consequences of malnutrition during treatment or about malnutrition in heterogeneous samples. In addition, nothing is known about the impact of malnutrition on children's functioning. The association between nutritional status and quality of life has never been studied in children with cancer.

Summary

Despite four decades of research on nutritional status in childhood cancer, some important questions still remain unanswered. We have identified the following gaps in current knowledge:

- clear prevalence rates of malnutrition are lacking, particularly in children with other malignancies than leukemia;
- the onset of under- or overnutrition and the course of the nutritional status are unknown;

- evidence for factors contributing to under- or overnutrition is lacking;
- consequences of malnutrition have not been studied in heterogeneous samples;
- the impact of nutritional status on quality of life is unknown.

HEALTH-RELATED QUALITY OF LIFE

During the past two decades, quality of life of children with cancer has become a critical issue in research. Survival rates have improved considerably and, consequently, more emphasis is placed on children's personal needs. Quality of life is a multidimensional construct that encompasses physical, mental, social, emotional, and behavioral components of well-being and functioning.[58] Health-Related Quality of Life (HRQOL) has a narrower focus and mainly emphasizes the impact of health (or illness) on the much broader concept of quality of life.[59,60] HRQOL in children and adolescents is complex because children mature and change. Children's physical abilities increase, and their understanding and perception of health and well-being also changes.[59] Physical abilities and family relationships may be very important to 8-years-olds; whereas body image, self esteem and peer relationships matter more to adolescents.[59] HRQOL is defined as "a multi-dimensional construct that includes physical, social and emotional functioning of the child, measured from the perspective of both the child and his/her family, and sensitive to the changes that occur throughout development."[61] Another definition includes children's perception of HRQOL: "an overall sense of well-being based on being able to participate in usual activities, to interact with others and feel cared about, to cope with uncomfortable physical, emotional, and cognitive reactions, and to find meaning in the illness experience."[62]

Since HRQOL is a subjective concept, the child itself is the preferred reporting source.[63] Children as young as 5 years old are able to communicate about their HRQOL.[64] Besides child self-report, parents can serve as their children's proxy reporters. The use of parent proxy-report is quite common in pediatric oncology, not only for children aged <5 years but also for older children and adolescents when they are not able to respond because they feel too ill. Moreover, parent proxy-report may contribute beneficial and complementary information toward a better understanding of the child's HRQOL. Therefore, HRQOL in children is preferably measured using both child self-report and

parent proxy-report.[63,65] In childhood cancer patients, parents' ratings of the child's HRQOL are generally lower than the child's ratings.[63,65] Parents are often better informed about the treatment and prognosis of their child's type of cancer, and they perceive cancer to have more negative consequences than children themselves. Moreover, parent's perception of their child's HRQOL may be biased by the burden of care-giving and their own well-being and concerns.[65]

Generally, it is assumed that HRQOL in undernourished children is lower than in well-nourished children and that improvement of the nutritional status will improve HRQOL.[39] In addition, overnutrition in healthy children has been linked to lower HRQOL as well. A literature review[66] revealed that obese children performed worse in the domains of physical, emotional, and social functioning compared with well-nourished children. Nevertheless, the association between nutritional status and HRQOL in children treated for cancer has never been researched.

THE PECANNUT STUDY

The PeCanNut study (Pediatric Cancer and Nutrition) is a prospective cohort study that aims to evaluate the nutritional status in children with cancer and to explore the impact of malnutrition on clinical outcomes and HRQOL. In

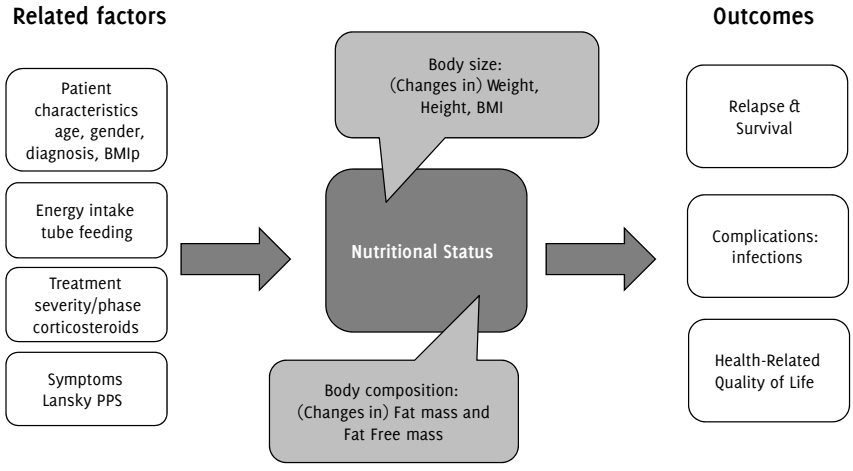


Figure 4. Flow-chart of the Pecannut study.

the period between September 2007 and December 2009, all children newly diagnosed with cancer that were consecutively admitted to the Department Pediatric Oncology and Hematology of the Beatrix Children's Hospital of the University Medical Center Groningen were asked to participate. Eligible patients were aged 0-18 years, had no prior diagnosis of cancer, were able

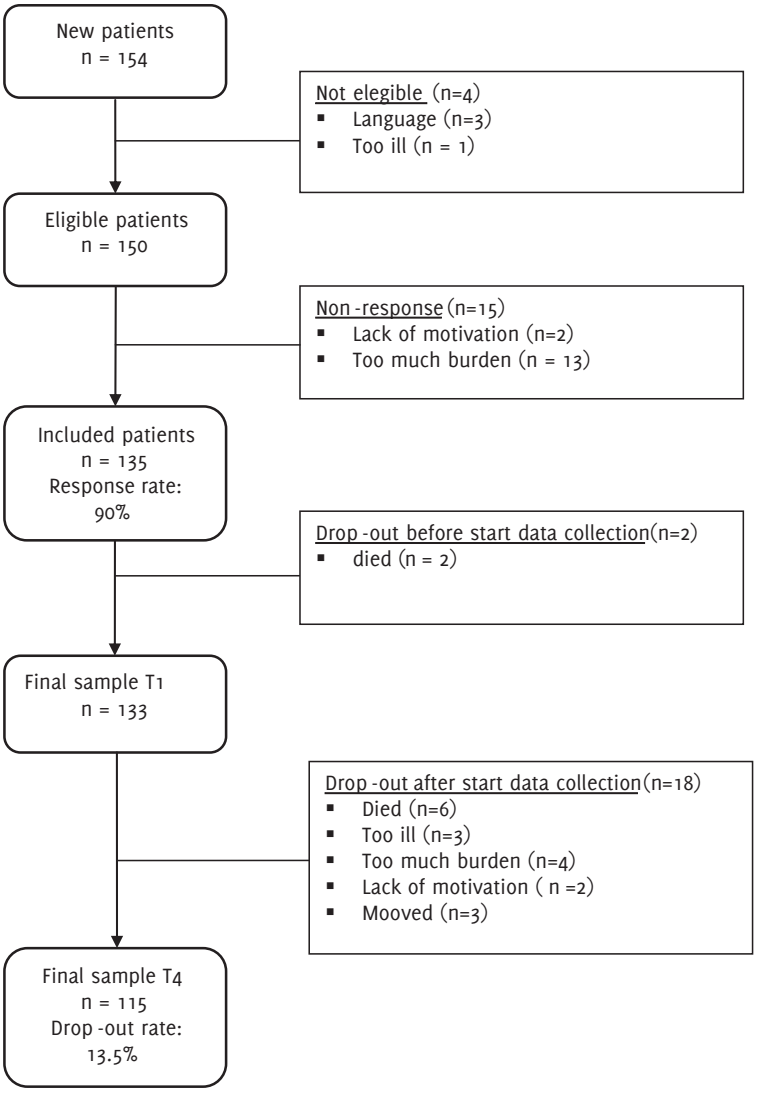


Figure 5. Research model Pecannut study

to understand the Dutch language, and received curative treatment. In this period, 150 patients met the inclusion criteria. Of these 150 patients, 135 gave informed consent, resulting in a response rate of 90%. After inclusion, two patients died, resulting in a total of 133 patients who participated in the study (See figure 4 for flow-chart Pecannut study). Not all patients participated in all parts of the Pecannut study. Some children only participated in measurements of nutritional status; whereas in other cases children were willing to fill out questionnaires and parents were not, or vice versa. The follow-up period was 12 months and ended in December 2010. During the follow-up period, 18 patients left the study because they became too ill (n=3), died (n=6), moved (n=3), felt too much burden (n=4), or experienced a lack of motivation (n=2) (drop-out rate 13.5%).

Figure 5 presents the research model of the Pecannut study. The central concept is the nutritional status that includes body size and body composition. The study's main focuses include changes in body size and body composition, factors related to those changes, and outcomes of under- and overnutrition. Measurements of nutritional status, related factors, and outcomes were performed at diagnosis, and at 3, 6, and 12 months after diagnosis. Within the first 3 months, weight, height, and mid-upper arm circumference were measured at 3, 6, and 9 weeks, because rapid changes are expected during this period.

AIMS AND OUTLINE

The general aim of this thesis is to evaluate the nutritional status in children with cancer. The more specific aims are: (1) to determine the prevalence of malnutrition; (2) to determine the onset of malnutrition and the course of the nutritional status; (3) to explore which factors contribute to changes in nutritional status; (4) to determine the clinical implications of malnutrition with regard to survival and infection risk; and (5) to determine the impact of nutritional status on HRQOL.

In **Chapter 2** a systematic literature review on the prevalence of undernutrition and the contributory factors to undernutrition in children with cancer is presented. Despite the large number of publications on undernutrition, a precise understanding of its prevalence and the patients at risk is lacking. Moreover, prevalence rates of industrialized and developing countries are also

often used indiscriminately. Therefore, the review is restricted to studies in industrialized countries so as to exclude other influencing factors such as poverty and lack of health care facilities. The focus of the factors that contribute to undernutrition lies on energy deficiency and inflammation.

In **Chapter 3** the nutritional status at the time of diagnosis is described. Not only actual values of weight and height are assessed, but also weight and height at diagnosis of cancer in relation to predicted data from children's growth curves.

In **Chapter 4** the changes in nutritional status during the 12 months after diagnosis are explored. Nutritional status is represented by body size (weight, height, and body mass index (BMI)) and body composition (fat mass and fat free mass). This chapter explores during which period of treatment changes in body size and body composition take place and which factors contribute to those changes. Included related factors are patient characteristics (age, gender, diagnosis, initial nutritional status, parental BMI), energy intake, oral or tube feeding, treatment intensity and treatment phase, corticosteroids doses, symptoms, and level of physical activity.

Dietary intake is a highly relevant factor for nutritional status. However, consensus is lacking on energy and protein needs of children treated for cancer. One of the main questions is whether energy and protein needs are increased or not. In **Chapter 5** the adequacy of energy and protein intake in children treated for cancer is assessed against three different norms: calculated individual requirements, recommended daily allowances, and intake in healthy controls.

In **Chapter 6** the clinical implications of malnutrition are examined. It has been hypothesized that undernourished children are more vulnerable to infections and have lower survival rates. In this study, all periods with febrile neutropenic episodes in the first year after diagnosis are analyzed and divided into fever of unknown origin or bacteremia. Complications are defined as admission to an intensive care unit or death. To define malnutrition, not only actual values of BMI are used as predictors, but also weight loss during the first 3 months of treatment.

Subjective measures, including measures of HRQOL, are prone to response shift bias; this means an individual's perception about good and poor HRQOL can change due to adaptation to the diagnosis of cancer. In **Chapter 7** the response shift phenomenon is studied in two frequently used measures of HRQOL: Cantril's ladder and the PedsQL measure. Moreover, similarities and differences with regard to response shift between child self-report and parent proxy-report were researched.

In addition to its clinical implications, a poor nutritional status can also influence a child's quality of life. Therefore, in **Chapter 8** the association between HRQOL and undernutrition, overnutrition, weight loss, and weight gain is studied. Moreover, nutritional status is examined in relation to the separate domains of HRQOL.

Chapter 9 is the concluding chapter in which the most relevant findings are summarized, the implications of the findings for clinical practice are discussed, and suggestions for future research are made.

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STATE OF THE ART OF MALNUTRITION

CHAPTER

2

MALNUTRITION IN CHILDHOOD CANCER PATIENTS: A REVIEW ON ITS PREVALENCE AND POSSIBLE CAUSES

Aeltsje Brinksma
Gea A. Huizinga
Esther Sulkers
Willem A. Kamps
Petrie F. Roodbol
Wim J. E. Tissing

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ABSTRACT

Purpose: to perform a systematic literature review for critical evaluation of prevalence and factors contributing to malnutrition in childhood cancer.

Methods: a systematic search resulting in 46 suitable articles.

Results: due to lack of uniform criteria and adequate studies, the prevalence rates of malnutrition can only be estimated. Based on strengths and weaknesses of included references, prevalence rates are estimated to be 0-10% for leukemia, 20-50% for neuroblastoma, and 0-30% for other malignancies. Whether energy deficiency or inflammation contributed to malnutrition could not be confirmed because the occurrence of energy deficit (low energy intake, increased metabolic rate) or inflammation (related to cachexia) was not convincing. Also, a relationship between these factors and malnutrition was not studied.

Conclusion: Longitudinal studies are needed to determine which children are at risk of malnutrition, and to investigate the impact of energy deficiency and inflammation on the nutritional status and body composition of childhood cancer patients.

INTRODUCTION

The nutritional status of children with cancer is highly relevant, since a good nutritional status enables them to cope better with the intensive cancer treatment regimens.[1-3] Moreover, malnutrition results in more complications, higher relapse rates, and lower survival rates.[2,4,5] Malnutrition is defined as follows: "A state of nutrition in which a deficiency of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form and function, and clinical outcome."[6] In order to prevent or adequately treat malnutrition in children treated for cancer, it is important to determine the extent of malnutrition and its contributing factors. Although publications on malnutrition in childhood cancer patients have appeared since the 1970s,[7] a precise understanding of its prevalence or of patients at risk is lacking. Reported prevalence rates are not only inconsistent and highly variable, but prevalence rates of industrialized and developing countries are also often used indiscriminately.[8,9]

As seen from its definition, malnutrition is amongst others caused by deficiency of energy, which means the energy intake fails to meet the energy requirement. This might occur because the energy intake is diminished, because the energy requirement is increased, or because both are altered. Another relevant factor that might contribute to malnutrition in (childhood) cancer patients is inflammation:[8,10,11] cytokines released by the tumor might alter protein, lipid, and carbohydrate metabolisms resulting in weight loss. This process is often described as cachexia which in turn is defined as: "A complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass."[12] Inflammation is one of the features of cachexia which is often seen in cancer patients.[8,13,14]

In theory, the factors contributing to malnutrition are clear. However, in practice it is more difficult to pinpoint which factors contribute substantially to weight loss and malnutrition in childhood cancer patients. If these factors could be clearly defined, interventions might be developed to prevent weight loss and malnutrition during treatment.

Therefore, the aim of this article is twofold: to perform a systematic literature review so as to critically evaluate (1) the prevalence of malnutrition, and (2) the factors contributing to malnutrition in childhood cancer patients. The contributing factors we will focus on are energy deficiency and inflammation. This review is restricted to studies in industrialized countries so as to exclude other influencing factors such as poverty and lack of health care facilities.

METHOD

Search strategy

A literature search was undertaken in the databases Pubmed, Cinahl, and EMBASE (only for inflammation) from 1951, 1981, and 1974 respectively till September 2010. The following search terms were used: Neoplasm [MESH]; free texts Cancer, neoplasm*, oncol*, Child* combined with:

- Nutritional Status: Meshterms: Body Size, Nutrition Assessment, Body Mass Index, Child Nutrition Sciences, Nutritional Status, Nutrition Disorders, Body Composition, Body Weight Changes, and free texts: body fat, lean body mass, fat free mass.
- Energy intake: Meshterms: Energy intake, Eating, Glucocorticoids, and free texts: energy intake, nutritional intake, dietary intake, energy intake, food intake, prednisone, dexamethasone, steroids, methylprednisolone.
- Physical Activity: Meshterms: Motor Activity, Exercise, Exercise Therapy, Physical Fitness, and free texts: physical activity, exercise, physical therapy, exercises, motor skills.
- Metabolism: Energy Metabolism and free texts: Cori cycle, citric acid cycle, glycolysis, energy metabolism, energy expenditure, basal metabolic rate, basal metabolism, metabolic rate.
- Inflammation: Meshterms: Cachexia, Inflammation, C-Reactive Protein, Tumor Necrosis Factor-alpha, Interleukin-1, Interleukin-6, Interferon-gamma, and free texts: cachexia, cachectic, inflamma*, c-reactive protein, tumor necrosis factor-alpha, interleukin-1, interleukin-6, interferon-gamma, CRP, TNF-alpha, IL-1, IL-6, IFN-gamma.

The searches were limited to children and adolescents (0-18 years). Only published data written in English or German were included, and additional literature was identified through the reference lists of these articles. Grey literature was not included.

Inclusion criteria

Studies meeting the following criteria were selected: studies on children 0-18 years diagnosed with cancer or undergoing cancer treatment in industrialized countries, and which described nutritional status, energy intake, basal or resting metabolism, physical activity, or inflammation related to malnutrition. Only studies with original data were included. Intervention studies manipulating intake or physical activity and studies describing inflammation in relation to infection were not included.

Table 1. Domains and items of methodological quality assessment

Domain	Items	Yes	No	Unclear
Contextual information	Clear description of the study (design, patient characteristics, age, sex, diagnosis, phase of treatment)	+	-	?
Selection bias	In- and exclusion criteria patient group defined, clear patient selection (random, consecutively, or all selected) Comparable control group	+	-	?
Outcome measurement	Cut-off values defined Valid measure Reliable measure	+	-	?
Results	Adequate report of results and control for confounder	+	-	?

Procedure

The search yielded 2477 studies (see Figure 1): after reading titles and abstracts 2033 were excluded. The excluded studies did not focus on nutritional status or on one of the causes of malnutrition in children with cancer. The remaining 444 were retrieved in full text, and out of these, 398 were not included as they failed to meet the inclusion criteria. Reasons for exclusion are mentioned in the footnote of Figure 1. Finally, 46 studies were included for this review.

Assessment of methodological quality

A gold standard for assessing the quality of observational studies does not exist.[15,16] Therefore, the reviewers selected domains that are important for the validity of the studies according to the procedure in the GRADE guidelines[17] and the Cochrane Handbook.[18] The quality of the studies was assessed based on contextual information, selection bias, validity and reliability of outcome measurement, results, and confounders (see table 1). For each domain a judgment was made whether all items were fulfilled (=yes), were not fulfilled (=no), or whether it proved impossible to make a proper judgment due to lack of information (=unclear). Two reviewers (AB and WT) independently assessed the quality of the 46 articles at the outcome level. Differences were solved by consensus. Following the procedure in the GRADE guidelines and the Cochrane Handbook, the quality ratings were not summarized, nor were cut-off values used to delete studies with low quality. This procedure of quality rating provides an impression of the quality of evidence with respect to the outcomes presented in this review. The results of the ratings are included in the Summary Tables 2-8).

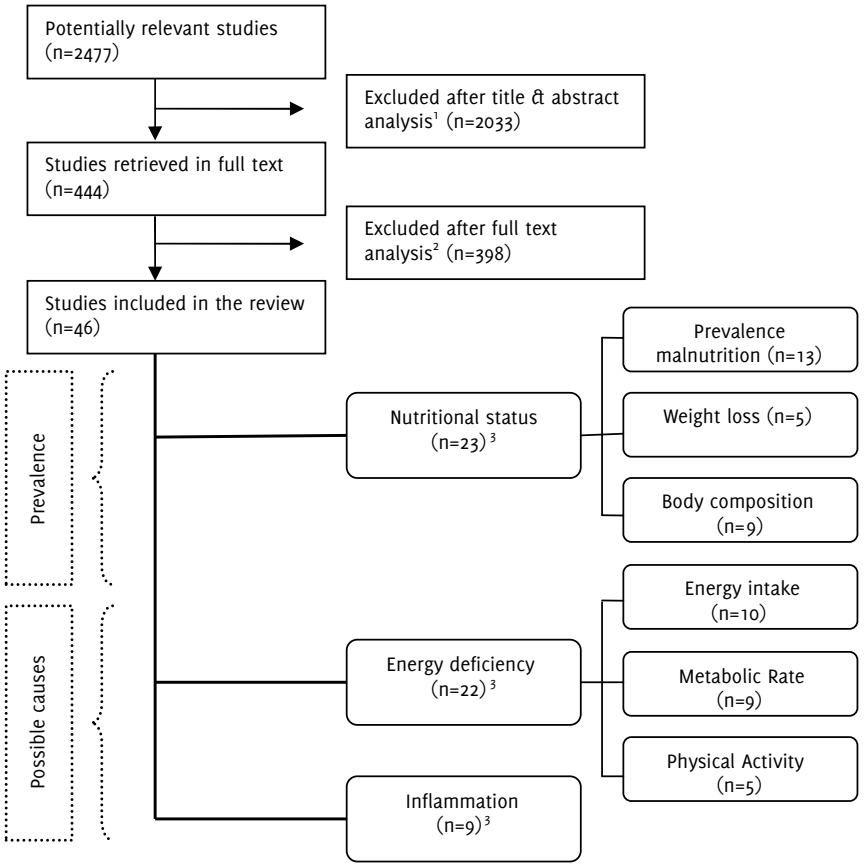

Figure 1. Flow of systematic literature review

[1]Excluded studies involved adults, survivors, patients in developing countries, no cancer patients, no nutritional status, nutrition in relation to risk of cancer, treatment/risk obesity, intervention studies concerning energy intake/physical activity, inflammation related to infection.

[2] After reading full text, the excluded studies did not meet inclusion criteria because this studies included survivors, or adults; this studies did not present original data of prevalence rates of malnutrition, weight loss, body composition, energy intake, metabolic rate, physical activity, or inflammation; this studies assessed energy intake related to obesity; this studies turned out to be intervention studies concerning energy intake or physical activity.

[3]Adding the number of studies describing nutritional status, energy deficiency, and inflammation exceeds forty-six as some studies describe more than one subject. The same applies to adding the number of studies describing malnutrition, weight loss, body composition, energy intake, metabolic rate, and physical activity.

ASSESSMENT OF NUTRITIONAL STATUS

Weight/height parameters

The nutritional status is generally expressed in weight, or weight in relation to height. In the literature, different indicators such as body mass index (BMI), weight-for-height (WFH), or ideal body weight (IBW) are used to determine the nutritional status. Malnutrition is determined using cut-off values expressed in percentiles, z-scores, ratios, or percentages. To determine which method should be used, it is important to take the clinical situation into account, since malnutrition as such is not important, but its clinical implications are. However, since data comparing the different criteria with outcomes, such as complications or survival rates, are lacking, it is impossible to say which method is superior.[19] This lack of a gold standard complicates the comparison between studies.

The most frequently used classification system, Waterlow,[20] distinguishes three grades of malnutrition: mild (80-90% of expected WFH[a]), moderate (70-80%), and severe (<70%). One of the disadvantages is that Waterlow assumes a stable weight/height ratio across all ages, which is not the case. Since the last decade, the classification of the World Health Organization (WHO)[21,22] is recommended defining malnutrition in: malnutrition (weight-for-age (WFA)<-2SDS); stunting (height-for-age (HFA)<-2SDS), and wasting (WFH<-2SDS). For international comparisons of prevalence rates of malnutrition the BMI cut-off value defined by Cole et al.[23] is recommended.

Weight loss

Next to actual values of weight and height, weight loss or decreased growth are also valuable indicators of malnutrition. Growth is important for children, since it is an essential feature of their health.[24] However, criteria for weight loss or decreased growth have seldom been used in the assessment of nutritional status in children with cancer. To date, weight loss is mainly described in the literature concerning failure to thrive[25,26] but not in the literature describing malnutrition.

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[a] Percentage expected WFH has been defined as actual weight divided by median weight at the given height x 100

Body composition

Body composition indicates nutritional stores and describes the percentages of fat mass (FM), representing fat stores, and fat free mass (FFM), representing the water and protein content of the body, including bone.[27] BMI is often used as a measure for body composition. However, this is incorrect because BMI does not distinguish between FM and FFM. Several methods have been developed to measure body composition.[28-30] These methods are based on different techniques and measure different elements of body composition. Dual-energy X-ray absorptiometry (Dexa), for instance, was primary developed to measure bone mineral mass,[31,32] but can also measure lean body mass and fat mass.[27,33] Isotope (deuterium) dilution is used to measure Total Body Water (TBW),[27,34] total body potassium counting is used to measure body cell mass,[35] and skin-fold measures and circumferences are utilized to assess fat mass. Information about body composition in children can be derived from all these techniques. However, it is difficult to determine which method is superior. All techniques have different pros and cons as Wells and Reilly have demonstrated.[28,29] The suitability of a given method depends on specific research questions and circumstances.[28,29] During childhood, simple techniques such as skinfold measurement or waist circumference may be more valuable than sophisticated techniques[28] if they are applied by experienced observers.

Serum levels

Serum proteins such as (pre-) albumin, retinol binding protein, and transferrin are used as indicators of nutritional status.[8,36] However, as serum protein levels may be altered by other factors such as infection, fever, and fluid shifts,[36-38] they are considered to be inappropriate measures for malnutrition in children and will therefore not be used as criteria in this review.

Body cell mass index

Recently, the validity of simple anthropometry to assess nutritional status was questioned in a study using body cell mass index (BCMI) measured with total body potassium counting as the reference measure for nutritional status.[39] This study concluded that weight/height parameters, arm anthropometry, and serum albumin could not accurately identify malnourishment in children with cancer. However, more research is needed to confirm these new findings and to determine the impact of low BCMI on patient outcomes. Therefore, we have chosen to use the anthropometric data to determine the prevalence of malnutrition of childhood cancer patients.

RESULTS: PREVALENCE RATES OF MALNUTRITION

A total of thirteen studies mentioned prevalence rates of malnutrition (see Table 2), both at diagnosis (10 studies), and during treatment (6 studies). Sample sizes varied from 10 to 1019 respondents. It is questionable whether accurate prevalence rates can be derived from small samples, because they cannot be easily generalized. However, given the limited number of studies and the good quality of some small sized studies, we have included all studies. The anthropometric data of the two largest retrospective studies[2,40] were extracted from medical records. In five studies[38,39,41-43] nothing was mentioned about the method used to obtain anthropometric data. In seven prospective studies[44-49] the data were collected by one or two persons. Obviously, the latter method is preferable for obtaining valid and reliable outcomes. Seven studies used the Waterlow classification. Unfortunately, a mutual comparison of these studies proved difficult because some studies[38,48,49] included only moderately and severely malnourished patients to determine the prevalence, while others[42-46] included mildly malnourished patients as well. Next we will discuss the prevalence rates of malnutrition for the different cancer types successively.

Prevalence of malnutrition

In **leukemia** patients, two retrospective studies reported prevalence rates *at diagnosis* of 7.6% in boys and 6.7% in girls in standard-risk ALL patients (n=1019),[40] and 10.9% in AML patients (n=768).[2] Because of the large sample size these prevalence rates appear to be valid. However, due to the retrospective data collection nothing is known about the reliability of the data. Also, because the latter study used BMI≤10th percentile as cut-off to define malnutrition, this resulted in higher prevalence rates since the 5th or 2.5th percentile are generally used.[6] Three prospective studies showed different outcomes. One controlled study in 173 ALL patients[45] presented prevalence rates of 6.9% including mildly malnourished patients, 18.4% according to TSFT, and 1.7% according to MUAC. Strikingly, the nutritional status of the ALL patients in this study did not differ from the nutritional status of 307 children admitted with other acute diseases. This indicates that malignant and benign acute diseases equally affected the nutritional status. The highest prevalence rate was reported in a controlled study in low-risk ALL patients:[44] 3 of the 15 (20%) appeared to be malnourished (two mildly (<85% WFH) and one moderately (<80% of WFH)). Despite the high prevalence rate, the

Table 2. Studies reporting prevalence rates of malnutrition

	Author	Quality[a] csor	Patients Dx	N, age	Time of Measurement/Method
Leukemia	Delbecque-Boussard[44] 1997 France	+?++	ALL standard- risk controls	15, 2-12y 15, 2-12y	T: at diagnosis, days 22, 36, 71 M: one observer
	Lange[2] 2005 US	++ -+	AML	768, 1-19y	T: at diagnosis M: records
	Reilly[40] 1999 UK	++?+	ALL standard-risk	1019, 0.4-14.9y	T: at diagnosis M: records
	Uderzo[45] 1996 Italy	++++	ALL controls	173, 2-15y 307, 5-14y	T: at diagnosis M: two observers
	Yu[46] 1994 US	+?++	Leukemia	25, 1-14y	T: at diagnosis (n=6), relapse (n=3) in remission (n=16) M: one observer
Solid tumor	Green[43] 2008 Canada	++? -	Neuroblastoma	10,1-5y	T: at diagnosis, after 2 courses of chemo, after surgical excision M: weight & height not mentioned; TSFT: one observer
	Rickard[41] 1983 US	+? - -	Neuroblastoma	18, 0-10y	T: at diagnosis, and during treatment M: not mentioned
	Schiavetti[47] 2002 Italy	++++	Solid tumors On-treatment Off-treatment	19, 4-15y 17	T: once in patients on-treatment and in patients off-treatment M: one observer

Method		Results	
Design	Criteria	At diagnosis	During treatment
PL co	%WFH <85% of French standards	20% (3 of 15)	unchanged during 71 days follow-up
RC nc	BMI ≤10th percentile	10.9%	
RC nc	BMI <-2 SDS	7.6% in boys 6.7% in girls	
PC co	%WFH<90% of median %TSFT<90 %MUAC<90	ALL vs controls 6.9% vs 8.5% 18.4% vs 11.4% 1.7% vs 1.6% Differences n.s.	
PC nc	%Wt <90 of median %Ht <90 of median %WFH <90 of median %TSFT <90 %MUAC <90 serum albumin <3.5g/dl	0%	0%
PL nc	%WFH[b] <85% serum albumin <32g/L TSFT <5 percentile High risk: two or more criteria are fulfilled	5 (50%)	3 (33%) after 2 courses of chemo and 2 (20%) after tumor excision
PL nc	Weight loss >5% WFH <5th perc Serum albumin <3.2 g/d Malnourished: one criterion fulfilled	50%	
PC nc	%RBW <90% BMI <5th percentile		Treatment group: 26.3% RBW 15.8% BMI none of the off-treatment group

Table 2 continued. Studies reporting prevalence rates of malnutrition

	Author	Quality[a] csor	Patients Dx	N, age	Time of Measurement/Method
Braintumor	Bakish[42] 2003 Canada	++?+	Medulloblastoma/ supratentorial PNET	103, 0-15y	T: at diagnosis, before & after surgery, radiotherapy, chemotherapy, dietic intervention, end of treatment. M: not mentioned
Mixed diagnosis	Merrit[38] 1985 US	-?+ -	ALL, solid tumors	90, 0-20y	T: weekly during 7 months. M: not mentioned
	Murphy[39c] 2009 Australia	??++	Not specified	40, 5.4-16.4y	T: 0.1 to 10.8 years since diagnosis M: weight, height, BCMI not mentioned, MUAC, TSFT one observer
	Pietsch[49] 2000 US	++?+	Hematological malignancies, solid tumors, brain tumors	127	T: at diagnosis M: records
	Smith[48] 1991 UK	++++	Leukemia, solid tumors, lymphoma Controls	100, 0.3-16y 55	T: at diagnosis, and at monthly intervals, controls only once M: one observer

Design: **P**= Prospective; **R**= retrospective; **L**= longitudinal; **C**= Cross-sectional; **co**= with control group; **nc**= not controlled.

Dx= diagnosis; **N**= number; **AMA**= arm muscle area; **BCMI**= body cell mass index (measured with total body potassium); **BMI**= body mass index: weight/(height)^2; **Dx**= diagnosis; **%IBW**= Percentage ideal body weight: measured weight expressed as a percentage of ideal weight based on the same height percentile; **MUAC**= mid-upper arm circumference; **%RBW**=relative body weight: (real weight divided by ideal weight at 50th percentile relative to age corrected for height) x 100; **SDS**= standardized deviation score; **TSFT**= triceps skin fold thickness; **WFH**= weight-for-height; **%WFH**= percentage weight-for-height: weight as percentage of median weight at the given height (Waterlow classification).

Method		Results	
Design	Criteria	At diagnosis	During treatment
RL nc	weight <90%IBW	31%	
PL nc	%WFH ≤80% of median AMA and TSFT: <5th perc serum albmine <2.8 gm/dl		29% one or more malnutrition values 10-20% all malnutrition indices
PC nc	Weight <90%IBW >5% weight loss BCMI z<-1.65 zBMI <-1.65 zMUAC, zTSFT <-1.65 Serum albumin		23% 3% 48% 7.5% 0%
RC nc	%WFH <80 of median WFH <-2 SDS BMI <-2 SDS	1% 1% 3%	
PL co	%WFH <80% of median TSFT <-2SD MUAC <5th percentile	Patients vs controls 5% vs 0% 23% vs 2% 20% vs 5% Differences significant	

[a] The quality of the studies was rated for the domains: c=contextual information, s=selection bias, o=outcome measurement, and r=results (see Table 1) and presented in this order. Meaning of the signs: + fulfilled; - not fulfilled; *?* unclear.

[b] %WFH= percentage weight-for-height: actual body weight/weight on same percentile as height (=Moore method).

[c] Same patients were described in study of Murphy 2010.[62]

mean values of the patients' nutritional status did not differ from that of 15 healthy controls. We believe the small sample size might have caused an overestimation of the prevalence rates in this study. Finally, the fifth study[46] found all anthropometric variables to be above the 90% in 25 standard-risk ALL patients, including only 6 newly diagnosed. This means the prevalence of malnutrition was 0%.

Unfortunately, little is known about malnutrition in ALL patients *during treatment*. With respect to the studies mentioned above, one study[44] mentioned that 3 of the 15 patients remained (mildly) malnourished, while the other study[46] found no malnutrition in ALL patients in remission.

In patients with **solid tumors**, three prospective studies with sample sizes <20 patients presented prevalence rates. Two of these studies reported prevalence rates of 50% in patients with neuroblastoma *at diagnosis*.[43,50] In one study, malnutrition *during treatment* decreased to 33% after 2 courses chemotherapy and to 20% after tumor excision.[43] In the other study the prevalence maintained 50%.[41] The high prevalence rates might be influenced by the use of more than one criterion, including serum albumin, to determine malnutrition. The third study[47] demonstrated prevalence rates of 26.3% according to %RBW and 15.8% according to BMI in patients with mixed solid tumors *during treatment*.

One study reported a prevalence rate of patients with **brain tumors** at diagnosis. In 103 patients with medulloblastoma and supratentorial primitive neuroectodermal tumors (PNET) 31% was found to be malnourished (WFH<90%) *at diagnosis*.[42] The percentage of patients mildly or moderately malnourished was not mentioned.

Finally, four prospective studies assessed the nutritional status in patients with **heterogeneous cancer types**. Unfortunately, the heterogeneity of the samples in these studies did hinder a derivation of clear prevalence rates for the separate cancer types. In a controlled study in 100 patients with leukemia and solid tumors,[48] 5% of the patients was malnourished at diagnosis according to WFH, 23% was malnourished according to TSFT, and 20% according to MUAC. The mean WFH ratio did not differ between patients and controls. However, the arm anthropometry results showed the nutritional status of the patients was worse compared to controls.[48] Thus, it was hypothesized that tumor mass masked the weight loss resulting in normal WFH and decreased arm circumferences. The second study in 90 patients with ALL and solid tumors[38] showed that at some point *during treatment*, 10% to 20% of the patients were malnourished according to weight/height, arm anthropometry and serum albumine, while 29% of the patients had low values for one or

more of these indices.[38] The third study in 127 patients with hematological, solid, and brain tumors,[49] presented prevalence rates of 1%, 1%, and 3% for %WFH, zWFH, and zBMI respectively. Mean values for some indices were lower in patients with solid tumors compared to patients with hematological tumors. The last study[39] found prevalence rates of 23%, 7.5%, 0%, and 0% according to %IBW, zBMI, zTSFT, and zMUAC respectively in 40 patients with oncological conditions requiring bone marrow transplantation.

Based on the strengths and weaknesses of the studies, we conclude the prevalence in leukemia patients is about 5-10% at diagnosis, about 0-5% during treatment, and that malnutrition prevalence does not deviate from that of children admitted with non-malignant diseases. It is almost impossible to summarize the prevalence rates for patients with solid tumors, since appropriate studies are lacking. Most sample sizes were either small, heterogeneous, or different criteria were used. The prevalence rates are probably higher than in leukemia patients. High prevalence rates were demonstrated in patients with neuroblastoma: 50% at diagnosis and 20-50% during treatment, although these high prevalence rates might be distorted by the use of more than one criterion and small sample sizes. For other patients with solid tumors the prevalence of malnutrition could only be guessed and might range from 0% to 30% at diagnosis and during treatment. Even less is known about patients with brain tumors. Only one study demonstrated that 31% of the patients with medulloblastoma and PNET was (mildly) malnourished at diagnosis.

Weight loss

Five studies reported weight loss in childhood cancer patients (see Table 3). Severe weight loss can be defined as >1-2% in 1 week, >5% in 1 months, and >7.5% in 3 months.[51] Eleven out of 19 patients with solid tumors had lost weight before diagnosis, of which 7 more than 5%.[52] Weight loss during treatment was demonstrated in patients with solid tumors[52,53] and patients with heterogeneous malignancies.[54] Unfortunately, no percentages were mentioned. Given the small sample sizes (n=14-21) these results should be interpreted cautiously. Weight loss during treatment was also described in patients with medulloblastoma.[42,55] In one study 46% of the 103 patients lost >5% of their initial body weight.[42] In another study, a mean weight loss of 8.2% was found in 41 patients with medulloblastoma during radiotherapy.[55]

Some cancer patients experienced weight loss before diagnosis and during treatment; this affected patients with solid tumors and medulloblastoma in particular.

Table 3. Studies reporting weight loss

	Author	Quality[a] csor	Patients Dx	N, age	Time	Design	Method Measure/criteria	Results
Solid tumors	Taskinen[52] 1998 Finland	+??+	Solid tumors	19, 1-14	At diagnosis and at monthly intervals during chemotherapy, 1-3d before surgery, one month after surgery.	PL	M: weight C: weight loss >5%	11 of 19 (57%) weight loss before diagnosis, 7 pat >5% weight loss. During treatment 1-2 months after surgery slight weight loss, no change in TSFT and MUAC, no change in muscle index.
Brain tumors	Bakish[42] 2003 Canada	++?+	Medulloblastoma supratentorial PNET	103, 0-15y	At diagnosis, before & after surgery, radiotherapy, chemotherapy, dietary therapy, end of treatment.	RL	M: weight C: weight loss/ gain >5%	Median weight change after surgery -0.35% ns; after radiotherapy -0.78% ns; after chemotherapy -4.35% sign; 46% lost >5% of their body weight.
	Ward[55] 2009 UK	+??+	Medulloblastoma	41, 2.2-19.8y	At diagnosis, post-surgery, during radiotherapy and up to 12 months post treatment.	RL	M: weight	Weight declined during radiotherapy, decline continued during chemotherapy: mean weight loss 8.23% (0-21%) since Dx.

Heterogeneous diagnosis	De Graaf[53] 1987 Netherlands	+?++	ALL Osteosarcoma Small round cell carcinoma	8, 4-13y 13, 11-37y 8, 3-24y	At diagnosis, after first part chemo.	PL	M: weight	In osteosarcoma patients sign weight loss (-2.4kg); in ALL and round cell carcinoma patients no sign weight changes.
	Skolin[54] 1997 Sweden	++?+	Leukemia, solid tumors, tumors CNS	14, 5-16y	At diagnosis, 1, 6, and, 3 months.	PL	M: weight	Weight at diagnosis -0.09; sign decrease after one week: -0.19 SDS; 6 weeks: -0.10 SDS; sign decrease 3 months: -0.37.

Design: **P**= Prospective; **R**= retrospective; **L**= longitudinal; **C**= Cross-sectional.

Dx= diagnosis; **N**= number; **Dx**= diagnosis; **C**= criterion; **CNS**=central nervous system; **M**= measure; **MUAC**= mid-upper arm circumference; **PNET**= primitive neuroectodermal tumors; **SDS**= standardized deviation score; **TSFT**= triceps skin fold thickness; **WFH**= weight-for-height; **%WFH**= percentage weight-for-height: weight as percentage of median weight at the given height (Waterlow classification).

[a] The quality of the studies was rated for the domains: c=contextual information, s=selection bias, o=outcome measurement, and r=results (see Table 1) and presented in this order. Meaning of the signs: + fulfilled; - not fulfilled; ? unclear.

Body composition

Most studies assessing the body composition in childhood cancer patients concerned ALL patients (see Table 4). Two studies used Dexa scans and demonstrated reduced FFM compared to reference values at diagnosis and during treatment.[56,57] Another study demonstrated a 27% decrease of muscle indices in 12 ALL patients within 4 weeks after diagnosis.[58] After 6 weeks the muscle index increased gradually. One study demonstrated similar patterns of muscle wasting in 12 ALL patients treated with corticosteroids and 8 children with other malignancies: muscle index decrease rapidly till week 6 and returned to almost initial level after 12 weeks of therapy.[59] Two studies found no decrease in FFM in 9 patients after bone marrow transplantation[60] or when compared to controls, found no differences in FFM at diagnosis or during treatment in 15 patients.[44] The FM, was normal at diagnosis [56] but increased

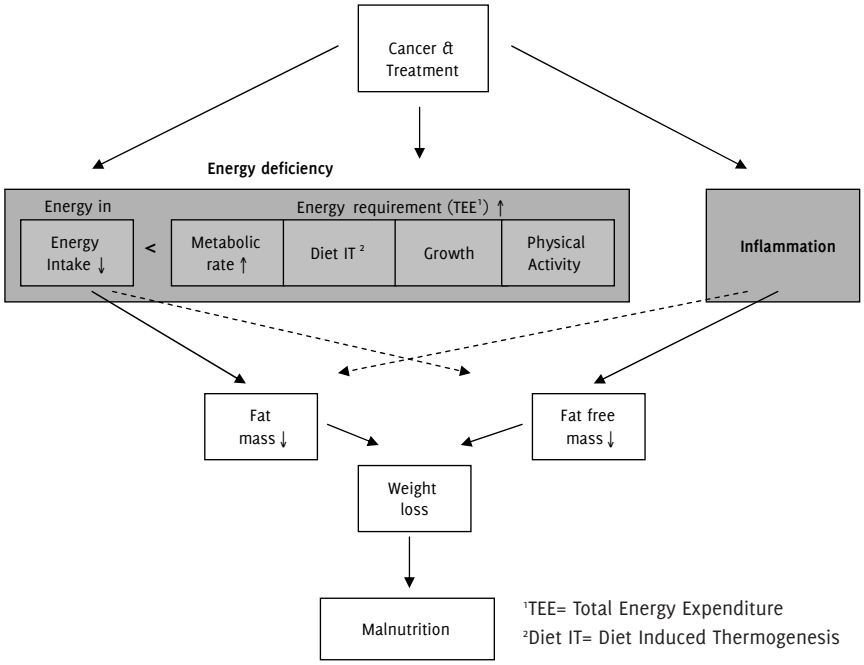

Figure 2. Conceptual framework of causes of malnutrition.
It is hypothesized that weight loss and malnutrition in cancer patients are induced by (1) energy deficiency and/or (2) inflammation. Due to low energy intake and increased metabolic rate, the energy requirement exceeds the energy intake resulting in loss of fat mass and to a lesser extent loss of fat free mass. Inflammation provokes loss of fat free mass, especially muscle mass, and sometimes fat mass is lost as well. *This model was adapted from Evans 2008[12] and Soeters 2009.[65]*

during treatment.[56-58,61]
A decline in FFM was also found in studies on patients with solid tumors.[52,53] In one group of patients (n=19), a declined muscle mass was found at diagnosis which remained low during treatment.[52] In patients with osteosarcoma (n=13), the deterioration of FFM during treatment was 10% more than predicted by weight loss.[53] In 40 children with heterogeneous malignancies, during treatment FFM did not differ from healthy controls while their FM was higher.[62]
To summarize: in patients with leukemia and solid tumors indications were found for reduced FFM at diagnosis and during treatment. During treatment the FM increased in ALL patients. However, the results should be interpreted cautiously, since different measures were used to determine the body composition and most studies were small sized.

RESULTS: POSSIBLE CAUSES OF MALNUTRITION

Energy deficiency

Energy deficiency is caused when the energy requirement exceeds the energy intake (see Figure 2). Energy requirement is expressed as Total Energy Expenditure (TEE) and consists of four elements.[63,64] First, the Basal Metabolic Rate (BMR) or Resting Energy Expenditure (REE), which is the minimum energy requirement needed to sustain life in a resting individual. In children and adolescents REE is the largest element of energy expenditure, representing 50-70% of TEE.[63] Second, the Physical Activity Energy Expenditure (PAEE): the energy required for physical activity. PAEE is the most variable element of the energy expenditure and accounts for 15-40% of TEE.[63] Third, the Diet Induced Thermogenesis (DIT): the energy needed for food processing. DIT is a rather stable element of the energy balance accounting for about 5-10% of TEE.[63] Finally, in children about 3% of TEE is needed for growth.[64] Energy deficiency leads to weight loss and to loss of fat mass in particular. Fat free mass is relatively spared because the body adapts to the energy deficiency by economizing its loss of proteins.[11,13,65] The literature suggests that decreased energy intake,[11,66] increased metabolic rate,[11,51,67,68] or altered physical activity might induce energy deficiency and result in weight loss. In the next section, we will discuss whether these assumptions can be substantiated on the basis of research in children with cancer.

Table 4. Studies reporting body composition

	Author	Quality[a] csor	Patients Dx	N, age	Time	Methods Design
Leukemia	Cheney[60] 1987 US	+ -?+	ALL	9, 12-35y	4 weeks after BMT	PL nc
	Davies[57] 2004 UK	+??+	ALL	14, 3.4-16.7y	At diagnosis, 6, 12, 24 months	PL nc
	Delbecque-Boussard[44] 1997 France	+?? -	ALL Controls	15, 2-12y 15, 2-12y	At diagnosis, days 22, 36, 71	PL co
	Halton[61] 1998 Canada	+??+	ALL	19	At diagnosis, every 12 months	PL nc
	Koskelo[58] 1990[b] Finland	+???	ALL, ANLL	12, 1-13y	At diagnosis, 2-4 week intervals till 24 weeks	PL nc
	Van der Sluis[56] 2002 Netherlands	+?++	ALL	61, 1.6-16.8y	At diagnosis, 6, 12, 24, 36 months	PL nc
Solid tumors	Murphy[62] 2010[c] US	+?++	Hematologic and solid tumors and controls	40, 5-16y 40	During treatment	PC co
	Taskinen[52] 1998 Finland	+?++	Solid tumors	19,1-14y 19 healthy controls	At diagnosis and at monthly intervals during chemotherapy, 1-3d before surgery, one month after surgery	PL co
Heterogeneous tumors	De Graaf[53] 1987 Netherlands	+?++	Osteosarcoma ALL Round cell sarcoma	8, 4-13y 13, 11-37y 8, 3-24y	At diagnosis, after first part chemo	PL nc
	Siimes[59 d] 1991 Finland	+++ -	ALL Controls: children with other malignancies	12, 1.9-13.5y For controls not described	At diagnosis, 2, 4, 6, 12, 16 weeks	PL co

Design: **P**= prospective; **R**= retrospective; **L**= longitudinal; **C**= cross-sectional; **co**= with control group; **nc**= not controlled. **Dx**= diagnosis; **N**= number; **BIA**= bio-electrical impedance analysis; **BCMI**= body cell mass index (measured with total body potassium); **Dexa**= dual-energy X-ray absorptiometry; **FFM**= fat free mass; **FM**= fatmass; **MUAC**= mid-upper arm circumference; **TSFT**= triceps skin fold thickness.

[a] The quality of the studies was rated for the domains: c=contextual information, s=selection bias,

	Results	
Measure	Fat Free Mass	Fat Mass
Isotope dilution	Loss body cell mass, no change in FFM.	No change in FM.
BMI, dexa	%FFM lower compared to reference at diagnosis and during treatment.	%FM sign increased at 6, 12, 24 months compared to normal and to Dx.
TSFT, biceps, subscapular, suprailiacal, BIA	At diagnosis not different from controls, no changes over time.	
Dexa	5% decrease at 6 months (ns).	Body fat increased from 22% at diagnosis to 28% at completion (ns).
Thickness of femoral quadriceps and of adipose tissue at the midway point of right thigh using ultrasound; circumferences of leg and arm	Muscle indices decreased 27% within first 4 weeks, after week 6 gradual increase.	Simultaneous increase of adipose tissue till week 12.
Dexa	Reduced at diagnosis, remained low during treatment, increased to normal one year after cessation of therapy.	Normal at diagnosis, fast increase in the first 6 months, decreased one year after cessation of therapy.
Total body potassium counting, air-displacement plethysmography Low FFM: BCMI z<-1.65 High FM: Male: %bodyfat >20% Female: %bodyfat >30%	Lower body cell mass than controls; lower FFM but not sign different from controls.	Higher than controls.
MUAC/TSFT Ultra sonography of femoral quadriceps muscle.	At diagnosis patients sign lower muscle mass than controls: 5.6 vs 8.5; no change in muscle index over time.	No difference in TSFT and MUAC between patients and controls.
Deuterium oxide.	Diminished 10% more than predicted by weight. no changes no changes	
Fat and muscle mass by ultrasound of quadriceps muscle	Muscle mass decreased rapidly till week 6, by week 12 returned to initial level. Control group (not treated with corticosteroids) had similar patterns for muscle mass.	

o=outcome measurement, and r=results (see Table 1) and presented in this order. Meaning of the signs:

+ fulfilled;

- not fulfilled; ? unclear.

[b] Same patients were described in study of Siimes 1991.[59]

[c] Same patients were described in Murphy 2009.[39]

[d] Same patients were described in study of Koskelo 1990.[58]

Table 5. Studies reporting energy intake

Author	Quality[a]	Patients			Method		Results	
	csor	Diagnosis	N, age	Time	Design	Measure/criteria		Nutritional status
Bond[72] 1992 UK	??++	ALL and solid tumors controls	26, 5-16y	At least 6 months after Dx, test before a block of chemotherapy and prednisone	PC co	M: Weighted intake during 7 days and checked during interview with dietician	Mean energy intake values similar to control group: patients 85% recommended daily amount, controls 87%. Range of energy intake larger in patient group. Seven patients reported less intake or slightly greater intake than BMR, none of these patients was malnourished.	Four patients malnourished: three <80% WFH, one <90% HFA.
Delbecque-Boussard[44] 1997 France	++++	ALL Controls	15, 2-12y 15, 2-12y	At diagnosis, day 22, 36, 71	PL co	M: 24-h recall C: <80% RDA	Energy intake was reduced at diagnosis and day 22 compared to controls, but disappeared by days 36 and 71. On day 1, 9 of the patients were consuming <80% RDA. On day 71, 5 patients had intakes <80% RDA and 4 of them had intakes >100% of the RDA.	Three patients malnourished WFH< 85% all the time, intake not different from other patients.
Smith[48] 1991 UK	++++	Leukemia, solid and brain tumors	62, 0.3-16.5y controls 23, 0.3-16y	At diagnosis	PC co	M: 24-h recall C: <80% RDA	27% of patients consumed <80% of RDA compared to 1% of controls. Median energy intake patients 90% (18-140) controls 99% (70-123) of RDA.	23% patients had TSFT<-2 compared with 2% controls; 20% pat MUAC<5th percentile none of controls; 11% pat AMA< 5th percentile compared with none of controls.
Carter[74] 1983 US	- - - -	Solid tumors hematopoietic malignancies	53, (18 follow up) 56, (25 follow up)	Start treatment & 6 months later	PL nc	M: 4-day dietary record (two week days + two weekend days) C: <80% RDA	The initial dietary intake of the cancer patients was about 80% of the RDA and very similar to general population. No differences between patient groups. After six months no change in energy intake.	Mean WFH ≥ 99, no change in 6 months. No relation between patients with inadequate intake and low weight/height percent.
Garcia[73] 1989 US	++ -+	Solid tumors, hematopoietic tumors, benign tumors	98, 7.9y	At diagnosis	PC nc	M: 24 h recall, a food frequency record, 4 day dairy C: <80% RDA	40.4% Inadequate calorie intake Mean calorie intake: 89.3% (±29.8) of RDA.	At Dx mean WFH: solid 104.6; hematopoietic 102.0; benign 96.2.

Halton[61] 1998[2] Canada	+? - -	ALL	16	At diagnosis and every 6 months	PL nc	M: Estimated food intake for 3-days	Nutrient intake was more than two thirds the recommended amounts for energy in 70% of the children. Intake remained constant over 2-year-period and was not related to decreased growth-velocity.	A reduced weight velocity was seen in 40% at 12 months and 14% at 24 months.
Kurugöl[75] 1997 Turkey	?? -+	Leukemia, bone tumors, and solid tumors	45, 1-18	25 pat in remission, 20 newly diagnosed	PC nc	M: Dietary intake history over 3 days C: <115% RDA	95% of patients consumed less energy than recommended, no difference in intake existed between remission and active disease group. Malnourished children consumed less than normal nourished children.	In remission group 44% were malnourished (24% advanced WFH <85%), in other group 60% malnourished (35% advanced).
Pedrón[76] 2000 Spain	+? -+	Several malignancies (autologous peripheral blood stem cell transplantation	34, 1.5-15.8y	Weekly after start therapy till 30 days	PL nc	M: 3 day record C: <80% estimated requirements (stress factor 1.4)	Before starting therapy the mean energy intake normal, 6 patients<80% of estimated requirements; no changes in mean energy intake over time except one day after transplantation.	Before start therapy 8 (23.6%) malnourished, 10 (29.4%) obese.
Skolin[54] 1997 Sweden	++ -?	Different malignancies	14, 5-16y	During 21 days starting at admission	PL nc	M: 7-day recording using household measures	The average intake decreased from 91% RDA before the start of chemotherapy to 65% in the third week after start of chemotherapy n.s. Intake during home days was higher: during hospital days the intake was 63% RDA, during home days 77% RDA.	The mean weight reduction after 1 week was 0.19 SD and after 3 months 0.37 SD.
Skolin[77] 2001 Sweden	++ -?	Different malignancies	11, 2-15	During treatment	PL nc	M: 7-day recording using household measures during 21 days	During hospital days average oral intake was 63% RDA. During home days average oral intake 75% RDA.	Compared with admission, weight reduction up to 3 months after start therapy (sign in first week with -0.29 SDS).

Design: **P**= prospective; **R**= retrospective; **L**= longitudinal; **C**= cross-sectional; **co**= with control group; **nc**= not controlled. **Dx**= diagnosis; **N**= number; **AMA**= arm muscle area; **C**=criterion; **HFA**= height-for-age; **M**=measure; **RDA**=recommended daily allowances; **SDS**= standardized deviation score; **TSFT**= triceps skin fold thickness; **WFH**= weight-for-height. [a]The quality of the studies was rated for the domains: c=contextual information, s=selection bias, o=outcome measurement, and r=results (see Table 1) and presented in this order. Meaning of the signs: + fulfilled; - not fulfilled; *?* unclear. Since RDA is an invalid criterion for determining the adequacy of the intake, the outcome measurement was rated as not fulfilled if RDA was used as the only criterion the determine the adequacy of the energy intake. [b]Study is not described in this review because it is not clear whether the energy intake has to be interpreted as adequate or not.

Energy intake

It is difficult to accurately assess the energy intake, because dietary data are prone to report errors, usually in the direction of under-reporting.[69] The 24-hour recall and the keeping of a dietary diary for three to four days were the most frequently used methods in the included studies. Although the diary method requires highly motivated respondents and more effort from the patient,[70] it is more reliable than the 24-hour recall because individuals tend to forget items.[71] Moreover, the representative of one-day-intake to determine the energy intake is questionable.[70] In general, the data concerning energy intake should therefore be interpreted with caution.

Most studies included in this review (see Table 5) used 80% of the recommended daily allowances (RDA) as a cut-off value to determine the adequacy of the intake. A better strategy is to compare the intake of childhood cancer patients with that of healthy controls, which was done in three studies. Compared with healthy controls, the energy intake of childhood cancer patients was lower at diagnosis.[44,48] In the first patient-control study, 27% of the 62 patients with various malignancies consumed <80% of the RDA at diagnosis, compared to 1% of the controls.[48] In the second study,[44] the energy intake of 15 ALL patients was lower compared to controls at diagnosis and on day 22. The energy intake of these patients improved over time, and after five weeks their intake no longer differed from that of healthy controls. In the third patient-control study[72] the mean energy intake of 26 patients (ALL and solid tumors) and controls was similar: 6 months after diagnosis patients consumed 85% of the RDA and controls consumed 87%. However, the range in energy intake in the patient group was larger.

In other studies conducted without healthy controls the results were not univocal. In patients with solid tumors and hematopoietic malignancies both inadequate intake (<80% RDA)[73] and normal intake[74] were reported at diagnosis. One study[75] found the intake of 95% out of 45 patients, newly diagnosed and in remission, to be below the recommended allowances (<115% RDA). Clearly, the higher cut-off value in this study strongly influenced the percentage of inadequate intake. In a longitudinal study in 34 patients undergoing autologous peripheral blood stem cell transplantation (PBSCT), the mean energy intake was normal throughout therapy, except at day +1 after PBSCT, while the energy intake of 6 (17.6%) patients was considered to be inadequate (<80% RDA including 1.4 stress factor).[76] Another study demonstrated that during hospital days the energy intake was lower (63% of RDA) than during home days (77% of RDA).[54,77] The use of various criteria to define the adequacy of the intake hampers a comparison

with the results of the non-controlled studies. Besides, the validity of the RDA as a criterion for the adequacy of intake is questionable. Notably, while in many studies the energy intake was found to be diminished, the protein intake was often adequate with regard to recommended allowances.[44,61,73,74]
Compared to healthy controls, the energy intake of childhood cancer patients seemed to be lower at diagnosis. In time, their intake improved and was comparable to the intake of controls; although still lower than the RDA. Apart from establishing whether the energy intake was lower than that of controls or lower with regards to RDA, the question is whether a decreased intake was associated with weight loss and malnutrition. Only one study tested this relationship and concluded that patients with an inadequate energy intake did not differ in nutritional status compared to patients who do have an adequate intake (n=109).[74]

Metabolic rate

Changes in metabolic rates have been reported among several adult patient groups. In comparison with controls, reduced, normal, and increased metabolic rates were found depending on the malignancy.[78] An increased metabolic rate contributes to weight loss and malnutrition. However, data assessing metabolic rate in children with cancer are limited. This is probably because the measurement is complex and burdensome, especially when young children are involved. Both BMR and REE were studied in children in order to determine the metabolic rate. Generally, REE tends to be 10-20% higher than BMR,[79,80] because the former is measured under less restricted conditions, for instance 4-6 hours after a meal instead of after an overnight fast.
All nine studies that determined the metabolic rate in childhood cancer patients, used small sample sizes (n=8-26; see Table 6). In two patient-control studies no increased metabolic rate could be demonstrated at diagnosis, or after three months in low risk ALL patients,[44] or six months after diagnosis in patients with ALL and solid tumors.[72] In children newly diagnosed with neuroblastoma and with an elevated heart rate due to catecholamine production of the tumor, increased REE could not be detected.[43] In patients undergoing allogeneic stem cell transplantation, REE decreased 14-20% when compared to nearly normal levels before transplantation, probably as a result of a decline in lean body mass.[81] In contrast, four studies reported increased metabolic rates before the start of chemotherapy:[82-85] One study[82] reported a higher REE in ALL patients with high tumor burden compared to patients with lower tumor burden. Yet another study[83] demonstrated an increased

Table 6. Studies reporting resting metabolic rate

Author	Quality[a]	Patients			Method	
	csor	Dx	N, age	Time	Design	Measure/criteria
Bond[72] 1992 UK	+?++	ALL or solid tumors and controls	26 26 5-16y	At least 6 months after diagnosis Test before a block of chemotherapy	PC co	M: indirect calorimetry
Delbecque-Boussard[44] 1997 France	+?++	ALL low-risk and controls	15 15 2-12y	At diagnosis, and at day 71	PL co	M: indirect calorimetry
Duggan[81] 2003 US	+?++	Stem cell transplantation (SCT)	25 1.3-19.1y	Before transplantation, weekly intervals during 5 weeks	PL nc	M: indirect calorimetry Reference value WHO and Schofield
Den Broeder[84] 2001 The Netherlands	+?++	Solid tumors	13 10-15y	At diagnosis, and twice during treatment	PL nc	M: indirect calorimetry C: BMR >110% reference value Schofield
Green[43] 2008 Canada	++++	Neuroblastoma	10 Mean 3.8y	At diagnosis, before starting chemotherapy, after two courses chemo, after surgery	PL nc	M: indirect calorimetry C: elevation of 25-30%; reference value WHO
Kien[85] 1987 US	+? - -	ALL	8	At diagnosis	PC nc	M: Indirect calorimetry C: Talbot 1938
Schmid[83] 2005 Germany	+?++	ALL and AML	15 0-15y	At diagnosis, before start treatment	PC nc	M: indirect calorimetry C: REE >110% reference value Fleisch and for infants Schofield
Stallings[82] 1989 Canada	+?++	ALL	9 6-15y	At diagnosis before the start of treatment, day 7, day 14	PL nc	M: open circuit indirect calorimetry C: reference value WHO 1985
Vaisman[86] 1993 Canada	+?++	ALL	8 7-18y	In the final 3 months of chemotherapy and 4 to 9 months after chemotherapy had been completed	PL nc	M: indirect calorimetry

Design: **P**= prospective; **R**= retrospective; **L**= longitudinal; **C**= cross-sectional; **co**= with control group; **nc**= not controlled. **Dx**= diagnosis; **N**=number; **BMR**= basal metabolic rate; **C**= criterion; **HFA**= height-for-age; **M**= measure; **MUAC**= mid-upper armcircumference; **REE**= resting energy expenditure; **SCT**= stem cell transplantation; **TSFT**= triceps skinfold thickness; **WBC**= white bloodcell count; **WFH**= weight-for-height; **WHO**= world health organization.

Results	
Metabolic Rate	Nutritional Status
No difference in BMR assessed at least 6 months after diagnosis and before a block of chemotherapy.	Four patients malnourished: three<80% WFH, one<90% HFA.
No differences in REE between patients and controls and no evidence for raised REE.	Three patients malnourished WFH<85%.
Baseline REE 95% of predicted values, decreased to 80% by week 3 after SCT, gradual increase in weeks 4 to 6.	After SCT decreases in weight and MUAC, TSFT unchanged.
BMR was 11.6% (s.d. 6.7%) than the estimated reference at diagnosis, and decreased to normal values after the first two courses of chemotherapy.	At Dx one patient WFH<80%.
No increased REE could be detected at diagnosis or after chemotherapy.	Five patients malnourished at Dx WFH < 85%/ TSF<5%/ albumine <32g/L, 3 remained malnourished at phase2, and 3 at phase 3.
Mean increase BMR 50% (sd34%) above reference values.	
Increased REE in 53%, mean REE 113% (s.d.17), hyper-metabolism correlated with tumor load.	No malnutrition at Dx, Metabolic rate did not influence nutritional status.
Patients with increased tumor burden (WBC & blast count) had increased energy expenditure at diagnosis. By day 7 and 14 differences between the groups with increased tumor burden and lower tumor burden were no longer apparent.	One child (low tumor burden) sign weight loss at Dx, the other 8 not. One patient (low tumor burden) WFH<80%.
No difference was found in REE during and after chemotherapy indicating that 6- Mercaptopurine (6MP) and Methotrexate (MTX) did not affect REE.	All had a good nutritional status.

[a] The quality of the studies was rated for the domains: c=contextual information, s=selection bias, o=outcome measurement, and r=results (see Table 1) and presented in this order. Meaning of the signs: + fulfilled; - not fulfilled; *?* unclear.

Table 7. Studies reporting physical activity

Author	Quality[1]	Patients			Method		Results	
	csor	Dx	N, age	Time	Design	Measure	Physical Activity	Nutritional status
Aznar[90] 2006 Spain	+?++	ALL 4-7 controls	7 7	One week during maintenance treatment	PL co	MTI Actigraph accelerometer	In ALL patients lower levels of total weekly time of MVPA were seen (328 ± 107min vs 506 ± 175min) and lower mean daily times of MVPA (49 ± 23min vs 79 ± 25min).	
Jacob[93] 2007 US	+ - - -	All diagnosis mean age	49, 12.5 ± 2.8 y	During treatment and admission max 5 days	PL nc	Numeric rating scale 0-10	At least 25% of the patients reported low activity levels ≤ 3.	
Jansen[92] 2009 The Netherlands	+?+ +	ALL controls	16, 4.2-15.3y 17, 4.0-16.7y	Maintenance phase 2 days during periods on-DEXA and 2 days off-DEXA	PL co	Pedometer Digiwalker and proxy report	PA was lower on-DEXA compared to off-DEXA. PA during on-DEXA was lower compared to controls, during off-DEXA PA was not sign different from controls.	Mean BMI Z-score was higher in patients than in controls: 1.1(±1.2) vs 0.2 (±1.1).
Sanford[91] 2008 US	+ - ++	ALL	88, mean 7.37y	During maintenance treatment: 5 days pre-dexa and 5 days during dexa	PL nc	Wristwatch Mini Motionlogger	No gender differences for daytime activity.	
Winter[94] 2009 Germany	+?++	All diagnosis controls	80, 45 5-18 y	7 days during active treatment during inpatient and home days	PL co	StepWatch Activity Monitor accelerometer	Patients were less active than controls. Patients were less active during inpatients days compared to home days, patients with bone tumors were less active than leukemia patients. Patients spent less time at high intensity level.	

Design: **P**= prospective; **R**= retrospective; **L**= longitudinal; **C**= cross-sectional; **co**= with control group; **nc**= not controlled.
Dx= diagnosis; **N**= number; **BMI**= body mass index; **Dexa**= dual-energy X-ray; **MVPA**= moderate-to-vigorous-activity; **PA**= physical activity.
[1] The quality of the studies was rated for the domains: c=contextual information, s=selection bias, o=outcome measurement, and r=results (see Table 1) and presented in this order. Meaning of the signs: + fulfilled; - not fulfilled; ? unclear.

REE (>110%) in 53% of the patients with leukemia, and found REE to be positively related to tumor burden. Increased BMR was also found in ALL patients, and proved to be related to increased rates of protein synthesis.[85] Patients with solid tumors had an increased metabolic rate at diagnosis as well.[84] After starting chemotherapy, the metabolic rate decreased.[82,84] This decrease was found to be associated with tumor response, and thus also with the effectiveness of therapy.[84] In contrast, a comparison of the metabolic rate during periods with and without chemotherapy revealed that chemotherapy did not affect the metabolic rate in ALL patients.[72,86] Only one study[83] reported the metabolic rate to be unrelated to nutritional status, while in the other studies a possible relationship between increased metabolic rate and weight loss was not researched.

To conclude, an increased metabolic rate during treatment could not be demonstrated in childhood cancer patients. Furthermore, the results concerning the metabolic rate at diagnosis were contradictory. Given the fact that all studies measured the metabolic rate appropriately using indirect calorimetry,[79] the differences in outcomes might be explained by the small sample sizes, the heterogeneous cancer types, and the comparison with a control group or an estimated reference value. The evidence for normal metabolic rate values seems to be more convincing, especially since this outcome was demonstrated in the two studies using a control group.

Physical Activity

Several studies examined PA in childhood cancer patients (see Table 7). Most studies used accelerometry; a method which measures movement directly, is capable of assessing the pattern and intensity of activity, is easy to use, and is unobtrusive.[87] Accelerometry is suitable for measurement in children and superior to more subjective measures like questionnaires.[88,89] The main impression conveyed by these studies was a reduced PA level during cancer treatment. Three studies used accelerometry to assess the PA level of ALL patients during maintenance therapy,[90-92] and found that patients were less active than controls.[90,92] The patients' level of PA appeared to be associated with the treatment phase: during treatment days on-dexa PA was lower than during days off-dexa,[91,92] and PA was lower compared to controls as well.[92] During days off-dexa, PA did not differ from controls.[92] A reduced PA level was also found in groups of patients with heterogeneous malignancies[93,94]. Accelerometry measurements showed that patients reached only 23% of the PA level of controls during hospital days and 40% during days at home. Patients

with bone tumors had distinctively lower activity levels than ALL patients.[94] Although five different studies demonstrated decreased PA levels, only one study mentioned a possible relationship to nutritional status. This particular study showed that both lower levels of PA and increases in BMI were demonstrated in ALL patients.[92] Unfortunately, this relationship was not tested.

Inflammation

Inflammation refers to the process of increased protein turnover and breakdown, increased lipid breakdown, and alterations in carbohydrate metabolism resulting in loss of muscle mass and body functions.[65,95] Sometimes fat mass is lost as well[12,13,96] (see Figure 2). Several parameters are used in the assessment of inflammation including C-reactive protein (CRP), and tumor released cytokines such as tumor necrosis factor α (TNFa) interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-γ (IFN-γ).[11-14,95-98] Unfortunately, these inflammatory markers are not exclusively related to cachexia. Increased levels might also be induced by infection[99,100] or chemotherapy.[101,102] Therefore, in the definition of cachexia increased inflammatory markers are only seen as diagnostic criteria when a weight loss of >5% is present.[12] Inflammation in relation to cachexia has hardly been studied in childhood cancer patients. We found four studies assessing both inflammation and nutritional status,[44,46,59,83] and two studies describing protein turnover.[85,103] Three other studies assessed inflammatory markers in isolation[102,104] or in relation to prothrombotic markers[105] (see Table 8).

One study[59] examined the relationship between TNF and cachexia in 12 newly diagnosed ALL patients. TNF levels were elevated at diagnosis and decreased gradually towards reference limits about 16 weeks after chemotherapy was initiated. Children with ALL and children with other malignancies (not treated with corticosteroids) demonstrated similar patterns of TNF serum levels and decrease of muscle index. No correlation could be demonstrated between individual TNF levels and muscle or fat mass. Other studies in patients with ALL[46,105], and Hodgkin lymphoma[104] found increased levels of inflammatory markers at diagnosis as well. In ALL patients the high levels gradually decreased during the induction phase, but remained higher than in controls.[105] Higher levels of cytokine antagonists TNF-RII and IL-1 receptors were found in children with a high white blood cell count, but these levels were not related to nutritional status.[83] Increased protein synthesis and breakdown were demonstrated in children with ALL, AML, and non-Hodgkin lymphoma at diagnosis when compared to controls.[85,103] Protein turnover

was related to increased metabolic rate.[85] However, no relationship was found between protein synthesis and breakdown and nutritional status.[103] On the other hand, in two studies inflammatory markers were undetectable or very low in both ALL patients during the first 10 weeks after diagnosis[44] and ALL and non-Hodgkin lymphoma patients in remission.[102]

Based on these studies, the presence of increased levels of inflammatory markers at diagnosis seems likely. However, the one study that did test relationship between levels of cytokines and nutritional status found no significant correlation.

Table 8. Studies reporting inflammation

	Author	Quality[a]	Patients			Method		Results	
		csor	Dx	N, age	Time	Design	Measure	Inflammatory activity	Nutritional status
Leukemia	Delbecque-Boussard [44] 1997 France	+?+ -	ALL low risk Controls	15, 2-12y 15, 2-12y	At diagnosis, days 22, 36, 71	PL co	IL-1β, IL-6, TNF, IFN- γ	Cytokine levels were undetectable.	3 of 15 WFH <85%
	Giordano[105] 2010 Italy	++++	ALL Controls	84, 1-17y 30, age matched	At diagnosis, day 24, 36, 52	PL co	TNF-a, IL-6	Highest levels at diagnosis, during treatment sign decrease, however levels remained higher than in controls.	
	Kien [85] 1987 US	+?+ -	ALL Controls	15, 3-15y 8, 4-17y	At diagnosis, 7 pat no chemo, 8 received prednison	PC co	Whole-body protein turnover using single dose [15N] glycine turnover technique	Protein synthesis and breakdown 59% and 100% increased compared to controls. Values in treated patients not different from controls. Protein synthesis and breakdown related to BMR r=0.93 and 0.91 respectively.	WFH patients <controls; 7/15 patients WFH <90%; 1/15 patients WFH <80%
	Schmid[83] 2005 Germany	+?++	ALL and AML Controls	22, 2-15y 25, 0-16y	At diagnosis before start treatment	PC co	sTNF-RII, IL-1a	Higher levels TNF-RII than controls. Patients with high tumor burden had higher TNF and lower Il-1a than patients with low tumor burden.	No relationship between cytokine antagonists and nutritional status
	Siimes[59] [b] 1991 Finland	+++ -	ALL Controls: children with other malignancies	12, 1.9-13.5y For controls not described	At diagnosis, 2, 4, 6, 12, 16 weeks	PL co	TNF Fat and muscle mass by ultrasound of quadriceps muscle	TNF levels were elevated at diagnosis and decreased gradually towards reference limits. Muscle mass decreased rapidly till week 6, by week 12 returned to initial level. In both groups similar patterns for TNF levels and muscle mass.	TNF levels not related to muscle or fat mass.
	Yu[46] 1994 US	+?++	Leukemia	25, 1-14y	At diagnosis (n=9), in remission (n=16	PC nc	CRP >1.5mg/dl	CRP in newly diagnosed patients > remission patients.	0% malnutrition

Leukemia & (non) Hodgkin	Ek[102] 2001 Sweden	+?++	ALL, non-Hodgkin	16, 2.5-14.8y	In remission prior to dose cytarabine	PL nc	TNF-α, IFN-γ, IL-6, IL-γ, IL-1β, IL-8, IL-10, IL-1ra	CRP level= 0, levels of interleukins undetectable or low. After administrating cytarabine the levels increased followed by fever.	
	Kien[103] 1983 US	+?++	ALL, AML, non-Hodgkin Controls	8, 7.9y 6, 10.8y	At diagnosis	PC co	Whole-body protein turnover using single dose [15N] glycine turnover technique	50-79% increase of protein synthesis and breakdown, higher than in controls.	No relations found between protein-synthesis/ breakdown and nutritional status.
	Wieland[104] 2003 Austria	++++	Hodgkin	95, 3.3-19.8y	At diagnosis	RC nc	CRP >5mg/L	At diagnosis 64% increased levels, CRP levels correlated with disease stage, stage I had lowest CRP level.	

Design: **P**= Prospective; **R**= retrospective; **L**= longitudinal; **C**= Cross-sectional; **co**= with control group; nc= not controlled.
Dx= diagnosis; **N**=number; **CRP**= C-reactive protein; **IL-1**= interleukin-1; **IL-1a**= inteleukin-1 receptor antagonist; **IL-1β**= inteleukin-1β; **IL-6**= interleukin-6; **IL-8**= inteleukine-8; **IL-10**= interleukin-10; **IFN-γ**= interferon-γ; **sTNFII**= soluble tumor necrosis factor receptor II; **TNF-α**= tumor necrosis factor α; **%WFH**= percentage weight-for-height: weight as percentage of median weight at the given height

[a] The quality of the studies was rated for the domains: c=contextual information, s=selection bias, o=outcome measurement, and r=results (see Table 1) and presented in this order. Meaning of the signs: + fulfilled; - not fulfilled; ? unclear.

[b] The same patients were described in the study of Koskelo 1990 [58].

DISCUSSION

Malnutrition

This is the first systematic literature review on the prevalence of malnutrition and its possible causes in childhood cancer patients. After more than three decades of research in malnutrition, it remains difficult to derive clear prevalence rates for the different cancer types and to define which children are really at risk. The limited number of studies, the generally small sample sizes, and the use of different methods and criteria to assess nutritional status, mean that it is almost impossible to present prevalence rates of malnutrition. Moreover, since most studies concerned children with leukemia, little is known about children with solid or brain tumors. Nevertheless, we conclude that leukemia patients run the lowest risk of malnutrition with prevalence rates of about 5-10% at diagnosis and 0-5% during treatment. The highest rate, 50%, was demonstrated in children with neuroblastoma. We estimate that depending on the method of measurement and cancer type, about 0-30% of the children with other solid tumors is at risk for malnutrition at diagnosis or during treatment. Even less is known about patients with brain tumors. Only one study demonstrated that 31% of the patients with medulloblastoma and supratentorial/PNET were malnourished at diagnosis.

Furthermore, since mild and moderate malnutrition were used interchangeably and various measures were used to determine malnutrition, the results should be interpreted cautiously. Until has been established which criteria are related to adverse outcomes such as complications and lower survival rates, it is impossible to draw conclusion about which method works best. Nevertheless, the use of uniform criteria might help to compare the results of different studies and to derive more unambiguous prevalence rates. Therefore, to enable a comparison we recommend the WHO classification[21,22] based on international data, and the BMI cut-off values defined by Cole et al.[23]

Weight loss was demonstrated in patients with solid tumors, medulloblastoma and heterogeneous diagnoses. Unfortunately, due to the lack of large longitudinal studies no conclusions could be drawn about the number and size of patients groups really at risk for weight loss during treatment. To date, in pediatrics weight loss is not used as a criterion for nutritional status, even though its negative consequences for the child's condition are evident. We suggest that weight loss is incorporated in the nutritional assessment.

Apart from changes in weight, changes in body composition were also found at diagnosis and during treatment. Indications for reduced FFM were found

in both patients with leukemia and patients with solid tumors at diagnosis and during treatment. This loss of FFM is alarming, because it deteriorates the child's condition and makes the child more vulnerable to complications such as infections.[106] Furthermore, it might lead to fatigue, reducing the child's quality of life.[12,95] During treatment, the decrease in FFM persisted, while the FM increased in ALL patients particularly.

Possible causes

To some extent, the factors leading to energy deficiency, such as low energy intake, increased metabolic rate, and altered physical activity (as described in the conceptual framework see Figure 2), have been studied in childhood cancer patients. The results for PA were clear: childhood cancer patients were less active. However, the results of the studies concerning low energy intake or increased metabolic rate were not univocal. In the controlled studies, energy intake of patients was lower at diagnosis compared to controls. Later on, during treatment, energy intakes were similar. The non-controlled studies reported merely inadequate intake compared to recommended allowances. The question remains how many calories should be recommended for childhood cancer patients especially since high levels of metabolic rate seemed to be present at diagnosis in particular. The evidence for normal metabolic rate was, however, more convincing. Low PA might have compensated for low intake and increased metabolic rate, thus preventing energy deficiency. This phenomenon is often seen in diseases in children and adults.[107,108] Although the presence of energy deficiency is likely in childhood cancer patients, only separate elements of the energy balance have been studied. It has never been studied in its entirety. So, whether the energy requirements exceeded the energy intake as hypothesized in the conceptual model (see Figure 2) could not be conclusively confirmed. Moreover, none of the studies tested the relationship between energy balance and nutritional status, so no conclusions can be drawn about the impact of energy deficiency on nutritional status. Other relevant factors which probably contribute to weight loss during treatment are enhanced losses due to vomiting, diarrhoea and malabsorption.[8] Nevertheless, these energy losses are relatively unimportant elements in the energy balance since there is little evidence for substantial influence.[63]

Generally, energy deficiency results in loss of FM and to a lesser extent FFM[109] (see Figure 2). However, the decline of only FFM at diagnosis and during treatment in patients with ALL and solid tumors stresses the relevance of diminished PA[108] (because low levels of PA may contribute to muscle wasting[110-112]) or

of cachectic processes above the presence of energy deficiency (see Figure 2). Several studies demonstrated increased levels of inflammatory markers at diagnosis and during treatment. However, in these studies a relationship with weight loss was not found. Probably, the studies were underpowered. Since the inflammatory markers are not exclusively related to cachexia, it remains difficult to confirm the presence of cachexia during treatment for childhood cancer. Furthermore, treatment with corticosteroids can cause muscle protein catabolism, which can in turn result in loss of FFM[68,95] and insulin-resistance resulting in increased adiposity.[113] It is worth noting that similar patterns of loss of FFM have been demonstrated in cancer patients regardless of whether they were treated with corticosteroids.[59] This might indicate that decreased PA is a major factor in the loss and the continuous low levels of FFM.

To summarize, the following three points seem to be essential. First, it proved difficult to derive clear prevalence rates of malnutrition since different criteria and cut-off values were used and appropriate studies are lacking. Longitudinal studies assessing nutritional status, weight loss, and body composition in heterogeneous cancer types both at diagnosis and during treatment are urgently needed.

Second, although some evidence was found for energy deficiency due to a decreased energy intake, low levels of physical activity might have compensated for that. More well-designed studies are needed to establish the energy needs of childhood cancer patients and to evaluate the consequences of energy deficiency on nutritional status. Furthermore, research is warranted to evaluate the impact of decreased physical activity on loss of muscle mass, muscle strength, and quality of life.

Third, due to the fact that the presence of inflammatory markers is not exclusively related to cachexia, and because no evidence was found for a relationship between inflammation and nutritional status, the presence of cachexia could not be confirmed. Again, more research is needed concerning the presence of inflammatory processes in childhood cancer patients, and the impact of inflammation on the nutritional status in order to develop adequate intervention strategies.

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PREVALENCE OF MALNUTRITION

CHAPTER

3

WEIGHT AND HEIGHT IN CHILDREN NEWLY DIAGNOSED WITH CANCER

Aeltsje Brinksma
Petrie F. Roodbol
Esther Sulkers
H. Louise Hooimeijer
Pieter J.J. Sauer
Eric van Sonderen
Eveline S.J.M. de Bont
Wim J.E. Tissing

Submitted

ABSTRACT

Background: In children, weight and height represent both nutritional status and growth. We aimed to determine weight and height at diagnosis of cancer in pediatric patients in relation to predicted data from these patients' growth curves.

Procedure: Actual data of weight and height of 95 children aged 1.5-10 years at diagnosis of cancer were compared with predicted data from growth curves. Age, gender, type of malignancy, extent of disease, and prior weight and height were tested for their potential relation to differences between actual and predicted data.

Results: Based on actual z-scores, 2%, 4%, and 7% of the children were undernourished (weight-for-age (WFA), height-for-age (HFA), and weight-for-height (WFH) <-2 standard deviation score (SDS) respectively). Actual data of weight and height were lower than predicted data. Differences of <-0.5 SDS in WFA, HFA, or WFH were found in 25%, 23%, and 29% of the children respectively. Children with advanced cancer had the highest risk of significant weight loss (<-0.5SDS in WFA) (OR_{WFA}=3.45 P=.012). Differences were unrelated to type of malignancy, age, gender, and weight and height prior to diagnosis.

Conclusions: At diagnosis, children's measurements of weight and height were lower than was expected from their growth curve. Even more importantly, according to loss of weight or lack of growth, more children were found to be poorly nourished. Thus, actual measurements of weight and height underestimated the deterioration in nutritional status. Therefore, growth history should be included in the assessment of nutritional status to detect whose nutritional status is at risk.

INTRODUCTION

Weight and height are important parameters to determine a child's nutritional status and represent the general impression of a child's growth. Nutritional status is determined by comparing measurements of weight and height with reference values of the population and is expressed in z-scores. A child is considered to be well-nourished when values of weight and height are within -2 and +2 standard deviation score (SDS) and undernourished when these values are below -2 SDS.[1]

However, data from one single measurement of weight and height do not adequately reflect the child's nutritional status. Children who suffer from severe weight loss or lack of linear growth but who nevertheless have what is considered normal weight and height parameters (between -2 and + 2 SDS) can still be undernourished. In fact, even obese children who have insufficient intake due to an illness and who subsequently experience significant weight loss can be undernourished,[2] for weight loss might result in loss of fat mass or fat free mass. As a result of weight loss, children lose muscle strength, suffer from fatigue, have lower tolerance for (chemo) therapy, and are more susceptible to infections.[3,4] Therefore, when a child is diagnosed with cancer, it is important to assess weight and height prior to the diagnosis, in addition to the assessment of actual values of weight and height. The inclusion of prior weight and height in the assessment of nutritional status will help clinicians to implement appropriate nutrition interventions.

To date, however, weight and height of children newly diagnosed with cancer are seldom compared with previous measurements. Literature reviews on undernutrition in childhood cancer patients[5] revealed that only one study reported weight loss at diagnosis;[6] whereas other studies only included actual values of weight and height to assess nutritional status at diagnosis.[7-10] In contrast, in adult cancer patients weight loss is seen as an important parameter for the assessment of nutritional status at the time of diagnosis. Moreover, weight loss is included in several nutritional screening tools for adults[11,12] and is found to have an adequate predictive value for classifying patients as undernourished or well-nourished.[13]

Determining weight loss in children is problematic because weight changes as a child grows. During childhood, average growth in weight is 2-3 kg each year. Until the start of puberty children grow 6-7 centimeters taller each year.[14] Hence, when comparing children's weight and height at diagnosis with prior data, this growth needs to be taken into account. A prolonged period of weight

maintenance or unchanged height should in fact be seen as deterioration in nutritional status. Another problem is that recent measurements of weight and height are usually not available. Moreover, parent-report of weight or height prior to diagnosis is not always reliable because of children's continuous growth.

In this study we used growth curves from preventive health care centers (PCHC) to predict the child's weight and height at diagnosis. Healthy children follow their individual growth curve until puberty.[15] In case of normal growth, data from the individual growth curve can be used to predict weight and height.[16,17] A difference between actual weight and height at diagnosis and predicted values may indicate lack of weight gain, lack of linear growth, or weight loss, all of which indicate deterioration in the child's nutritional status. This study has two main objectives. First, we aimed to compare actual weight and height at diagnosis with predicted weight and height based on the child's growth curve. Second, we aimed to assesses whether differences between actual and predicted data are related to age at diagnosis, gender, type of malignancy, extent of disease, and weight and height prior to diagnosis.

METHODS

Participants

The patients in this study were recruited from two prospective cohort studies (Pecannut study[18] and Clep2 study, data not yet published) conducted at the University Medical Center Groningen (UMCG) in the Netherlands between 2007 and 2013. Children whose data on weight and height were available from PCHC records were included. In addition, only pre-pubertal children (according to Tanner I[19]) aged <11 years were included. This inclusion was based on the fact that during puberty children frequently divert from their growth curves due to growth spurts. This diversion is mostly unrelated to changes in their nutritional status. Exclusion criteria were being non-Dutch speaking or being in a palliative phase of treatment at the time of enrollment. For both studies written informed consent was given by all parents. Both studies received ethical approval from the Medical Ethics Committee of the UMCG.

Measures and procedures

At diagnosis, measurements of actual weight and height were performed.[20] Details regarding measurements have been published previously.[18] In addition, data of weight and height were obtained from PCHC records. These data are routinely collected by health care professionals in children between the ages of one month and 4 years. All data were converted into z-scores according to Dutch reference standards for weight-for-age (WFA), height-for-age (HFA), and weight-for-height (WFH).[14] To determine the children's own growth curve prior to their diagnosis, the mean value of the z-scores for weight and height of children between 1.5 and 4 years of age was calculated (Fig. 1). This mean z-score represents the child's nutritional status prior to diagnosis and is called predicted z-score. From the age of 1-1.5 years onwards children have their own growth curve, and studies have demonstrated that they follow

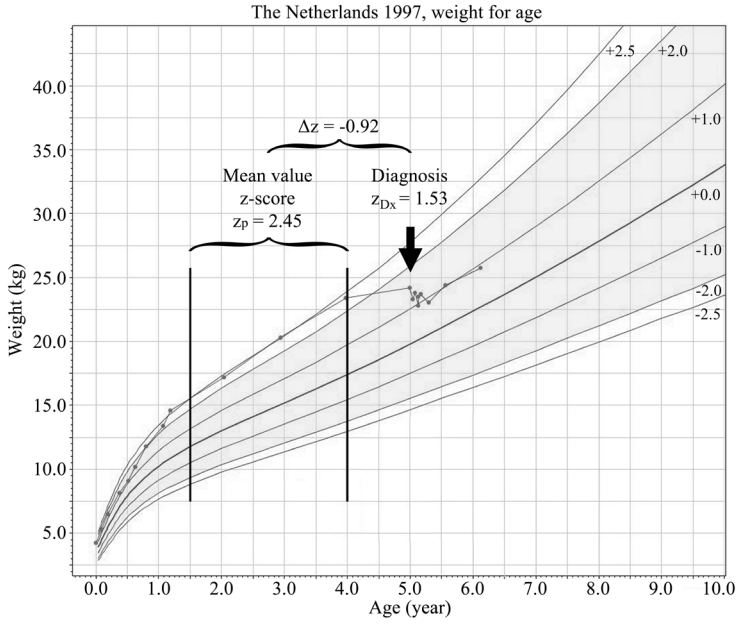

Figure 1. Example of a weight-for-age growth curve of a boy diagnosed with cancer at the age of 5 years. Difference in z-score Δz is: z-score at diagnosis z_{Dx} minus predicted z-score z_p (=mean value of z-scores at age 1.5-4 years).

their curve fairly closely until they reach puberty.[16,21] For patients aged ≥1.5 years at diagnosis, all measurements (minimum of 2 measurements) were used to compute the predicted z-score; whereas for children aged 1.5 years at diagnosis the mean values of the last two measurements were used. To determine differences between actual and predicted WFA, HFA, and WFH, change in z-score (Δz-score) was computed as: z-score diagnosis - z-score predicted.

Since weight loss of >5% during the first 3 months of treatment was found to be clinically relevant in childhood cancer patients on-treatment,[22] we considered a difference of 5-10% between predicted and actual data of weight and height to be relevant at diagnosis. This criterion of 5-10% is also used in adults.[23] A weight loss of 5-10% corresponds to a difference of about 0.5 to 1 SDS in weight. These differences were found to be clinically relevant for height as well.[24]

For children aged up to 5.0 years at diagnosis, the period between the last measurement at a PCHC at the age of 4 years and diagnosis did not exceed 12 months. For children >5.0 years at diagnosis, this period varied between 1-7 years. Greater differences are to be expected over a longer period of time; therefore, to control for whether the length of time since the last measurement at a PCHC influenced the magnitude of differences, the Δz-scores were first computed for two age groups: children aged ≤5.0 years and children aged >5.0 years at the time of diagnosis. In case the two groups did not differ, further analyses were conducted for the whole group.

Differences in weight and height were evaluated in relation to age, gender, type of malignancy (hematological, solid, and brain), extent of disease, and weight and height prior to diagnosis. Extent of disease was divided into localized or advanced stage (defined as leucocytes $>100x10^9$/l in leukemia, metastasis in solid and brain malignancies, stage III and IV in lymphoma).

Statistical analyses

Since we expected weight and height at diagnosis to be lower than predicted, one-sided dependent t-tests were used to compare actual z-scores for WFA, HFA, and WFH with predicted z-scores for WFA, HFA, and WFH. Two-sided independent t-tests were performed to compare Δz-scores for children aged ≤5.0 years and children aged >5.0 years, and Pearson Chi-square was performed to compare percentage children with Δz <-0.5 SDS in both groups. In order to explore the relation between Δz and age, gender, and prior weight and height, Pearson correlation coefficients and independent t-tests

were conducted. Analysis of variance (ANOVA) was used to compare the Δz between the three types of malignancies. Odds ratio were calculated to determine the association between extent of disease and Δz. Significance of OR was tested by Pearson Chi-square. Given that the number of respondents was fixed at 95, statistical power was sufficient for an effect size of 0.25 (β=0.80; α=0.05). P value <0.05 was considered statistically significant.

RESULTS

Respondents

The patient group consisted of 95 children, of which 45 (47%) were girls. The median age was 5.4 years (range 1.7-10.8). Patients were diagnosed with hematological (57%), solid (26%), and brain malignancies (17%) (Table 1).

Actual and predicted weight and height

According to actual z-scores at diagnosis, 2% (2/95) were underweight (zWFA<-2 SDS), 4% (4/95) showed stunting (zHFA< -2SDS), and 7% showed (7/95) wasting (zWFH<-2 SDS) (Fig. 2).

The Δz-scores for WFA, HFA, and WFH of the age groups ≤5 years and >5 years did not differ (independent T-test all P values >0.05). Therefore, data of both groups were analyzed together. Actual z-scores for WFA, HFA, and WFH were lower than predicted z-scores (dependent T-test all P values <0.05, Table 2).

Differences in weight and height

Differences of <-0.5 SDS were found in 25% (24/95) of the patients for WFA, 23% (22/95) for HFA, and 29% (28/95) for WFH (Fig. 2). Differences of more than 1 SDS were found in 8% percent (8/95), 9% (9/95), and 16% (15/95) of the patients for WFA, HFA, and WFH respectively. The percentage of children with Δz <-0.5 SDS did not differ between the age groups ≤5.0 years and >5.0 years (Pearson Chi-square all values >0.05).

Factors related to differences from growth curves

Correlation coefficients revealed that differences in WFA, HFA, and WFH were not related to age at diagnosis (Pearson r= -0.024, 0.013, -0.031 respectively, all P values >0.05) or to nutritional status prior to diagnosis

Table 1. Characteristics of the respondents (n=95).

Characteristics			
Median age (range)	5.4 (1.7-10.8)		
	n (%)		
Age , 5.0 years	44 (46)		
Age › 5.0 years	51 (54)		
Gender: female	45 (47)		
Diagnosis	**Extent of disease n (%)[a]**		**n (%)[b]**
	Localized (n=70)	Advanced (n=25)	Total
Hematological	43 (80)	11 (20)	54 (57)
Leukemia	40	5	45 (47)
Lymphoma	3	6	9 (10)
Solid tumors	14 (56)	11 (44)	25 (26)
Neuroblastoma	2	7	9 (10)
Wilms tumors	4	2	6 (6)
Bone	5	1	6 (6)
Solid other	3	1	4 (4)
Brain tumors	13 (81)	3 (19)	16 (17)
Medullo- and	2	2	4 (4)
ependymoblastoma	5	0	5 (5)
Astrocytoma/glioma	6	1	7 (7)
Other			

[a] % refers to percentage patients of the diagnosis group
[b] % refers to the total patient group

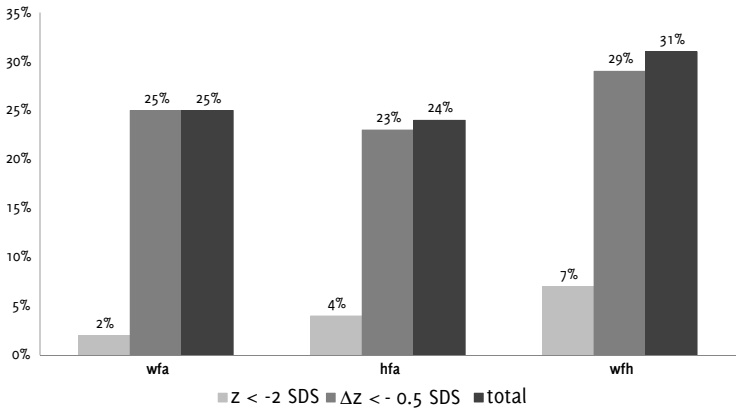

Figure 2. Percentage of patients (n=95) with z <-2 SDS, Δz <-0.5 SDS, and the total percentage of patients with actual low values for weight and height or significant differences. WFA, weight-for-age; HFA, height-for-age; WFH, weight-for-height; Δz-score: z-score diagnosis – predicted z-score; SDS, standard deviation score.

Table 2. Predicted z-score, z-score at diagnosis and difference in z-score: $\Delta z = z_p - z_{Dx.}$ Mean (SD) are presented.

		Predicted z-score growth curves	Actual z-score at diagnosis	Δ z-score	P value[a]	Effect-size[b]
All patients	zWFA (SD)	.09 (.94)	-.14 (1.03)	-.23 (.55)	0.002	.39
n=95	zHFA (SD)	.11 (1.08)	-.10 (1.20)	-.22 (.61)	0.020	.33
	zWFH (SD)	.07 (.84)	-.13 (1.12)	-.20 (.85)	0.047	.23
Hematological	zWFA (SD)	-.00 (.88)	-.17 (.95)	-.17 (.40)	0.002	.39
n=54	zHFA (SD)	.02 (1.02)	-.11 (1.08)	-.13 (.46)	0.020	.28
	zWFH (SD)	-.00 (.81)	-.17 (1.02)	-.17 (.74)	0.047	.23
Solid	zWFA (SD)	.31 (1.09)	-.09 (1.22)	-.40 (.67)	0.003	.52
n=25	zHFA (SD)	.29 (1.26)	.07 (1.39)	-.22 (.60)	0.038	.35
	zWFH (SD)	.24 (.94)	-.21 (1.15)	-.45 (.88)	0.008	.47
Brain	zWFA (SD)	.07 (.93)	-.10 (1.06)	-.18 (.74)	0.177	.24
n=16	zHFA (SD)	.14 (1.00)	-.34 (1.34)	-.49 (.99)	0.031	.46
	zWFH (SD)	.03 (.79)	.15 (1.37)	.12 (1.06)	0.327	.12
Localized	zWFA (SD)	.03 (.93)	-.11 (.97)	-.14(.48)†	0.007	.29
stage	zHFA (SD)	.06 (1.03)	-.12 (1.21)	-.17 (.60)	0.009	.28
n=70	zWFH (SD)	.03 (.83)	-.07 (1.05)	-.09(.80)‡	0.119	.12
Advanced	zWFA (SD)	.26 (1.00)	-.21 (1.21)	-.47(.67)†	0.001	.58
stage	zHFA (SD)	.26 (1.21)	-.07 (1.22)	-.33 (.66)	0.009	.46
n=25	zWFH (SD)	.18 (.85)	-.31 (1.28)	-.49(.93)‡	0.008	.47

[a] *P* values based on one-sided Paired T-tests. [b] Effect-size based on Cohen's r; effect sizes are designated as small (0.10), medium (0.30), and large (0.50). †These values differ significantly according to independent T-test. ‡These values differ significantly according to independent T-test. y, years; SD, standard deviation; zWFA, z-score weight-for-age; zHFA, z-score height-for-age; zWFH, z-score weight-for-height.

(Pearson r= -0.126, -0.067, -0.124 respectively, all P values >0.05). No differences were found between boys and girls (independent t-test zWFA t= -.161, zHFA t=-.269 zWFH t=-.399, all P values >0.05).
Both patients with hematological and solid malignancies had lower z-scores for WFA, HFA, and WFH at diagnosis than predicted (Table 2). In patients with brain malignancies weight remained stable; whereas height at diagnosis was almost 0.5 SDS lower than the predicted height (Table 2). ANOVA analyses revealed that the three diagnosis groups did not differ with regard to the differences between actual and predicted z-scores ($ANOVA_{(Welch\ statistic)}$ WFA F=1.299, HFA F=1.121, WFH F=1.777, all P values >0.05.).
Differences in Δz-scores for WFA and WFH were greater in patients with advanced stage cancer compared with localized stage (independent T-test values P<0.05, Table 2). Advanced stage was associated with higher risk of significant weight loss (<-0.5SDS) (OR_{WFA}=3.45 P=0.012; OR_{HFA}=1.42 P=.504; OR_{WFH}=2.45 P=0.063). Children with localized or advanced stage did not differ with regard to predicted or actual z-scores (Independent T-test, all P values >0.05).

DISCUSSION

This is the first study to use data from growth curves to determine weight loss, lack of weight gain, and lack of linear growth in children newly diagnosed with cancer. Comparison of weight and height at diagnosis with data from growth curves indicated that, on average, children's weight and height at diagnosis was lower than predicted. At diagnosis for cancer, children were lighter, smaller, and thinner than expected. Based on actual z-scores, 2%, 4%, and 7% were undernourished at diagnosis for WFA, HFA, and WFH respectively. However, compared with their growth curves another 20-24% of the children lost more than 0.5 SDS in WFA, HFA, and WFH. In fact, children's actual nutritional status at diagnosis was worse than the actual data of weight and height indicated. As such, the actual data of weight and height underestimated the deterioration in nutritional status. Therefore, prior weight and height need to be taken into account when determining the nutritional status of pediatric patients. A child with significant weight loss (for instance, >0.5 SDS in 1 month) might be more at risk of adverse health outcomes than a child who grows along the -2 SDS WFA curve. Moreover, since children with cancer undergo intensive treatment and often experience weight loss,[18]

it is of the utmost importance to detect those children that are already poorly nourished at the time of diagnosis. A comparison of actual values of weight and height with predicted values will not only detect more children at risk of undernutrition, but is also more in line with common practice in pediatrics. However, clinical professionals face the problem of how to determine loss in weight and height at a given time point, for instance, at diagnosis of cancer. The current study offers a potential method to solve this problem.

The differences between actual and predicted weight and height were the same for boys and girls and independent of the child's previous weight and height. Thus, children with low values for WFA on their growth curves were not more susceptible to weight loss than children with high values for WFA. Contrary to another study,[25] which found higher risk of undernutrition in younger children after hospital admission, including children diagnosed for cancer, the current study found no relationship between age and undernutrition.

In patients with hematological and solid malignancies, significant losses in WFA, HFA, and WFH were demonstrated. Despite loss in HFA, loss in WFH was significant as well. This means that, proportionally, loss in weight was more severe than lack of linear growth. According to the literature,[4,26] children with advanced cancer stage experienced more severe weight loss and their risk of <-0.5 SDS weight loss was more than three times larger than in children with localized cancer. This weight loss prior to diagnosis may be due to diminished energy intake or increased energy requirements. Many patients experience a period of illness and/or nausea prior to diagnosis, resulting in diminished intake. Additionally, tumor mass causes alterations in metabolism which can result in increased energy expenditure.[27-30] These alterations may particularly concern children with advanced cancer. However, the factor that contributes most to weight loss has not yet been identified.

In contrast to patients with hematological and solid malignancies, WFA and WFH remained stable in patients with brain malignancies; whereas a significant loss of almost 0.5 SDS in HFA was found in this particular patient group. Literature has shown that diminished growth can be one of the early signs of brain tumors. Diminished growth has been found in patients with tumors in the hypothalamic region such as craniopharyngioma[31] and in patients with brain stem tumors such as astrocytoma and glioma.[32] Imbalances in growth hormones may play a role here.

A point for discussion is which differences in weight and height are clinically relevant and cause health risks such as infections, and lower survival rates. The most specific criteria define significant weight loss as >2% in 1 week,

>5% in 1 month, >7.5% in 3 months, and >10% in 6 months.[33] Strikingly, in pediatric oncology these criteria have been used only once.[34] A disadvantage of using %weight loss over a prolonged period of time is that the real weight loss is underestimated because normal growth during that period is not taken into account. Since z-scores consider growth, the z-score is a better indicator to detect differences in weight and height over time and should therefore be preferred to %weight loss. To define clinically relevant cut-off values for losses in WFA; HFA; and WFH, differences in z-scores should be related to outcomes such as morbidity; mortality; and quality of life.[35,36] To date, one study has demonstrated an increased infection rate in childhood cancer patients with >5% weight loss in 3 months compared with their weight at admission.[22] Rapid weight loss seems to make these children more vulnerable to bacterial infections. Thus, >5% or >0.5 SDS weight loss appears to be clinically relevant. Considering these important finding, more studies that address the clinical relevance of weight loss are needed.

An additional finding of this study was lack of linear growth in patients with hematological and solid malignancies. Considering the acute nature of these malignancies weight loss is to be expected. However, the relatively lower height at diagnosis reveals that some of these children may have suffered from poor health for a longer period of time, which suggests that the cancer process was present long before diagnosis.

The results of this study are based on the assumption that children follow their own growth curve until the onset of puberty.[15] The difficulty with this assumption is that the present growth curves have been developed using cross-sectional data, while longitudinal growth curves that determine variation in growth over time are scarce. The question whether children really follow their own growth curve remains unanswered as yet. The few studies on this phenomenon found that in infancy[16,17] and puberty[17] z-scores regressed to the mean and deviated considerably. However, after infancy until puberty children maintained their growth curve and there was no regression to the mean.[16,17] Another study[37] found horizontal height tracks in a majority of pre-pubertal children, indicating that those children maintained their growth curve.

This study has demonstrated that data from one single measurement of weight and height are insufficient to obtain a valid impression of a child's nutritional status at the time of cancer diagnosis. The actual data of weight and height underestimated the deterioration in nutritional status. In contrast, the inclusion of predicted weight and height based on growth curves resulted in the identification of nearly 25% more children with a poor nutritional status

than a classification based on actual values alone. Children with advanced cancer had the highest risk of weight loss. Although the onset of cancer is considered to be acute and is associated with loss in weight, lack of linear growth was also found in this study. In conclusion, in addition to actual weight and height at diagnosis, comparison of weight and height at diagnosis to a child's growth history, is urgently recommended to detect those children whose health is at risk and to implement timely intervention measures.

Acknowledgements

We are very grateful to all children and their parents for participating in the Pecannut study and Clep2 study, and we wish to thank Sonja Hintzen of the University Medical Center Groningen for her constructive advice and editing service, and we wish to thank Thijs de Bont of the University Medical Center Groningen for his graphical support.

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PREVALENCE AND RELATED FACTORS OF MALNUTRITION

CHAPTER

4

CHANGES IN NUTRITIONAL STATUS IN CHILDHOOD CANCER PATIENTS: A PROSPECTIVE COHORT STUDY

Aeltsje Brinksma
Petrie F. Roodbol
Esther Sulkers
Willem A. Kamps
Eveline S.J.M. de Bont
Annemieke M. Boot
Johannes G.M. Burgerhof
Rienk Y.J. Tamminga
Wim J.E. Tissing

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ABSTRACT

Background & aims: Under- and overnutrition are linked to adverse outcomes during and after childhood cancer treatment. Therefore, understanding the timing of weight loss and weight gain and their contributory factors is essential for improving outcomes. We aimed to determine in which period of treatment changes in nutritional status occurred and which factors contributed to these changes.

Methods: A prospective cohort study of 133 newly diagnosed cancer patients with hematological, solid, and brain malignancies was performed. Anthropometric data and related factors were assessed at 0, 3, 6 and 12 months after diagnosis.

Results: Despite initial weight loss at the beginning of treatment in patients with hematological and solid malignancies, body mass index (BMI) and fat mass (FM) increased within 3 months with 0.13 SDS ($P<0.001$) and 0.05 SDS ($P=0.021$) respectively. Increase continued during the following months and resulted in a doubling of the number of overnourished patients. Fat free mass (FFM), which was already low at diagnosis, remained low. During the entire study period about 17% of the patients were undernourished on the basis of low FFM. Tube feeding and diminished activity level were related to increases in BMI and %FM respectively. No relationship was found between energy intake or corticosteroids and increase in BMI or %FM.

Conclusions: BMI and FM increased during and after the period of intensive treatment, while FFM remained low. Improvement of nutritional status might be accomplished by increasing physical activity from the early phase of treatment.

INTRODUCTION

Poor nutritional status is linked to adverse outcomes both during treatment of childhood cancer and during survivorship. During cancer treatment under- and overnutrition result in more complications, higher relapse rates, and lower survival rates.[1,2] During survivorship, overnutrition is one of the risk factors for diabetes mellitus type II, hypertension, and cardiovascular diseases.[3] This is especially a problem in cancer survivors, who run the additional risk of developing cardiovascular disease due to treatment with potential cardiotoxic chemotherapy or radiotherapy.[4] Undernutrition in the general population is also associated with morbidity and increased all-cause mortality.[5] Although previous studies have presented data of under- and overnutrition in childhood cancer patients, little is known about the timing of the onset of under- and overnutrition and their respective causes. It is therefore necessary to study the timing and the causes of changes in nutritional status in order to develop adequate intervention strategies.

Nutritional status can be represented by both body size and body composition. Body size is measured using weight, height, and body mass index (BMI), and represents the general impression of the child's growth. Body composition is expressed in fat mass (FM) and fat free mass (FFM), which represent the nutritional stores of the body.[6,7] Body composition can be measured both by complex methods, such as air-displacement plethysmography (ADP) or simple methods such as bioelectrical impedance analyses (BIA). Patients can be undernourished because of low BMI and/or low FFM, or overnourished because of high BMI and/or high FM. Both criteria are not necessarily present at the same time. For example, low FFM can be present in patients with normal BMI. In this study both body size and body composition are considered to be relevant.

Presumably, changes in nutritional status are caused by the malignancy or its treatment and continue into survivorship. Therefore, it is important to gain insight in the course of weight loss or weight gain and changes in body composition during treatment, but also to determine the factors related to these changes. Up till now, most studies assessing nutritional status relied on cross-sectional data.[7] The few prospectively conducted longitudinal studies that did report on changes in nutritional status predominantly concerned patients with acute lymphoblastic leukemia (ALL) and described time intervals of 6 months or more, making a detailed analysis of the timing of changes difficult.[8,9] Longitudinal studies in patients with solid and brain malignancies

are scarce.[7] Therefore, we conducted a prospective cohort study among newly diagnosed cancer patients with heterogeneous malignancies and registered body size, body composition, and related factors during 12 months after diagnosis. Our research questions were:
In which period of treatment do changes in body size and body composition arise?
Which factors contribute to those changes in body size and body composition?

METHODS

Participants

All children newly diagnosed with cancer, who were consecutively admitted to the Pediatric Oncology Department of the University Medical Center Groningen (UMCG) between September 2007 and December 2009 were asked to participate in a prospective cohort study called the Pecannut (Pediatric Cancer and Nutrition) study. The follow-up period was 12 months and ended in December 2010. Eligible patients were between 0 and 17.99 years of age, had no prior diagnosis of cancer, had sufficient command of the Dutch language, and received treatment with curative intent. In total, 150 patients were eligible for inclusion. Fifteen patients refused participation because they found the study too burdensome (n=13), or because a lack of motivation (n=2) (response rate 90%). After inclusion, 2 patients died before assessments, resulting in a total of 133 patients who participated in the study. Patients were divided in three groups: hematological, solid, and brain malignancies. Ethical approval was obtained from the Medical Ethics Committee of the UMCG, and parents and children aged ≥ 12 years gave their written consent.

Procedure

Nutritional status was assessed within one week after diagnosis and at 3, 6, and 12 months after diagnosis by two trained observers. In addition, weight, height, and mid-upper arm circumference (MUAC) were measured at 3, 6, and 9 weeks. Measurements of the patient characteristics were taken at diagnosis; the other related factors were assessed simultaneously with the measurements at diagnosis, 3 months, 6 months, and 12 months. The follow-up measurements were taken mostly during visits to the outpatient department

and between courses of chemotherapy to make study participation more acceptable to patients.

Measures

Nutritional status

Weight was measured using a calibrated digital scale and recorded to the nearest 0.1 kg (for infants to the nearest 0.01 kg). During measurements children only wore underwear. Height was measured using a calibrated digital stadiometer or an infantometer for infants, and recorded to the nearest 0.1 cm. MUAC was measured halfway between the tip of the acromion and olecranon process using a non-stretchable measuring tape SECA 212 to the nearest 0.1 cm. Triceps skinfold thicknesses (TSF) was measured as a proxy for FM. TSF was measured using a Harpenden skinfold caliper in the same region and recorded to the nearest 0.1 mm. Both measures were performed in duplicate on the left arm. Data were expressed as standard deviation scores (SDS) calculated from Dutch reference standards.[10,11] These Dutch reference standards were based on data of the fourth nationwide growth study performed among 14,500 healthy children[10] and a study population of 2,333 healthy children.[11] Furthermore, FFM was determined by bioelectrical impedance analyses (BIA) using a 50 kHz frequency BIA (BIA 101, Akern, Italy). BIA was performed on the left side of the body with the patients in supine position, arms and legs apart, in the absence of fever, intravenous hyper-hydration, and edema. To calculate FFM, the equation of Goran was used.[12] Subsequently, FM and %FM were calculated. FFM, FM, and %FM were also expressed as SDS using Dutch reference values.[13] Undernutrition was defined as BMI<-2SDS or FFM<-2SDS, overnutrition as BMI>2SDS or FM>2SDS, and relevant weight loss or weight gain was defined as >5% change between 2 sequential measurement times.

Related factors

Patient characteristics

The patient characteristics included in this study were age, gender, diagnosis, initial nutritional status and body composition, and parental BMI.

Energy intake

Energy intake was assessed using a 3-day dietary diary and total kcal was calculated using food calculation software (Eetmeter 2002, The Netherlands Nutrition Centre, The Netherlands). Percentage intake of individual energy requirement (using Schofield's formula[14]) was calculated. In addition, it was

registered whether the child received oral or tube feeding.

Treatment intensity and treatment phase
Treatment intensity was rated with the Intensity of Treatment Rating scale (ITR-3).[15] Since only a few patients were rated either in the least intensive or most intensive categories, the ITR-scale was reduced to two categories: least/moderate intensive and very/most intensive. Furthermore, at each measurement time it was recorded whether a patient was still in active treatment or whether therapy was terminated.

Cumulative dose of corticosteroids
Based on treatment protocol the cumulative dose of corticosteroids (mg prednisone/m^2) was calculated. To calculate the corresponding dose of dexamethasone, a conversion of 6.67 was used. Corticosteroid use after brain surgery was included as well.

Symptoms
The Memorial Symptom Assessment Scale (MSAS)[16] was used to assess symptom frequency and symptom distress. Moreover, we derived two subscales from MSAS: a 13 item scale with feeding related symptoms and a 2 item scale assessing nausea and vomiting (Crohnbach's α of the 3 scales was within 0.76 and 0.90) (see supplement for items of both subscales).

Physical activity
The level of physical activity was assessed using the Lansky Play Performance Scale (PPS).[17] This is a 10-point parent-rated Likert-scale that records the daily play activity of the child ranging from completely disabled (10) to fully active (100). PPS was considered as a surrogate measure for physical activity.

Data analysis and statistics
To answer the first research question, analyses were performed for the period of intensive treatment (0-3 months) and for the usually less intensive period of maintenance treatment (3-12 months). The number of patients with relevant weight loss or weight gain and prevalence rates of under- and overnutrition was calculated. Differences between patients with oral or tube feeding were tested with independent T-tests and Chi-square.
Multilevel analyses were performed to determine: 1) whether parameters of body size and body composition changed over time; 2) whether the three

patient groups differed with regard to body size and body composition; 3) whether the three patient groups differed with regard to changes over time; and 4) which factors contributed to the changes in body size and body composition. In these fourth multilevel analyses, BMI SDS and %FM SDS were the dependent variables that represented body size and body composition respectively.[7] Related factors were entered in the analysis using backward selection and were tested for main effects and interaction with time. Since BMI and %FM were the dependent variables in the analysis and could not be used as covariates as well, MUAC SDS at diagnosis was used as a substitute for initial body size and BMI SDS at diagnosis for body composition. As BMI showed a parabolic curve trajectory between 0-3 months and a linear trajectory between 3-12 months (Figure 2c), data of BMI were analyzed for two separate periods: 0-3 months, including all measurement times between 0-3 months (time-square term was included and time was centered), and 3-12 months, including the measurements at 3, 6, and 12 months. In order to build a powerful model, analyses of %FM covered the whole period of 0-12 months. Analyses of body composition were restricted to children ≥ 4 years old due to the lack of valid regression equations to calculate FFM and FM from BIA outcomes. Multilevel analyses were performed using linear mixed models of SPSS 20 and likelihood ratio tests were used to determine the best multilevel solution. *P* values <0.05 were considered statistically significant.

RESULTS

Characteristics of the cohort

A total of 133 patients with hematological (39.8%), solid (33.1%), or brain (27.1%) malignancies were included in the study. Their median age was 8.1 years (0.1-17.7) and 52.6% were female (Table 1). During the study period, 18 patients left the study because they became too ill (n=3), died (n=6), moved (n=3), felt too much burden (n=4), or experienced lack of motivation (n=2) (drop-out rate 13.5%) (Figure 1). The 9 patients who left the study because of death or increased severity of illness, had a worse nutritional status compared with those who remained in the study (BMI at diagnosis = -1.38 SDS versus BMI=0.00 SDS Mann-Whitney-U=304, P=0.023; FFM=-1.89 SDS versus FFM=-0.67 SDS Mann-Whitney-U=86, P=0.021).

In total, 60 (45.1%) patients received (naso) gastric tube feeding for several

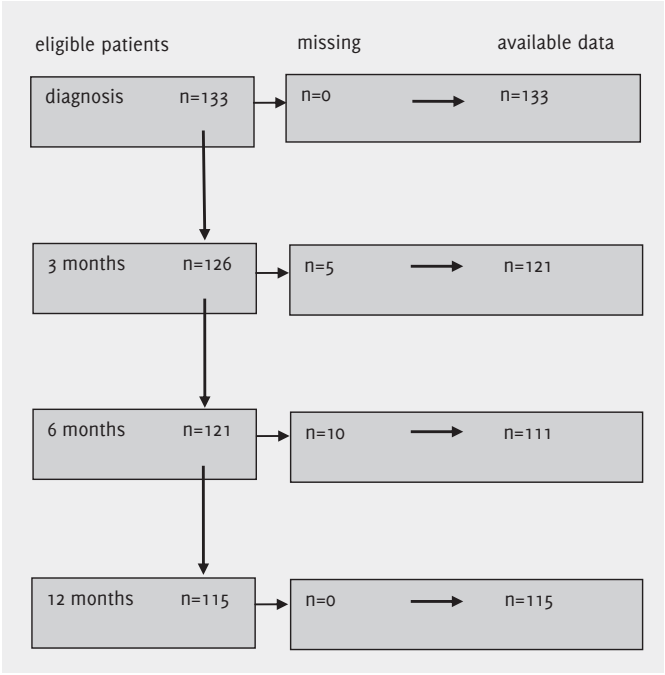


Figure 1. Flow chart of follow-up. Reasons for loss to follow-up (n=18) were: child became too ill (n=3), died (n=6), moved (n=3), felt too much burden (n=4), or experienced lack of motivation (n=2).

days or weeks at any given time during the first year. These patients were younger (mean age 7.2 years versus 9.6 years t=2.832 P=0.005), had lower initial weight (mean weight-for-age (WFA)= -0.27 SDS versus WFA= 0.20 SDS t=2.151 P=0.033), and underwent more intensive treatment (χ^2=24.5, df=2, P<0.001) than patients without tube feeding. Mean percentage energy intake (of individual requirements) for the whole study period was 105% (SD 38%). Energy intake decreased over time from 111% at the beginning of treatment to 96% after 12 months (estimate multilevel analysis = -1.46 (95% CI -2.38, -0.54), P= 0.002).

Changes in body size

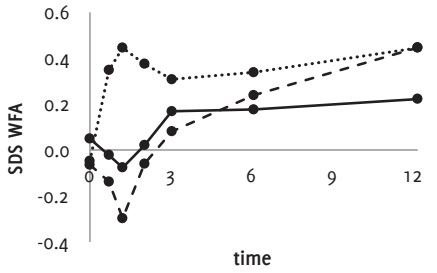
0-3 months

During the first 3 months after diagnosis, relevant weight changes (>5%) were found in 63.7% (n=79) of the patients (Table 2). Weight loss was prevalent in patients with hematological and solid malignancies; whereas the majority

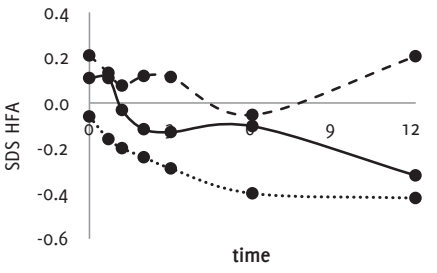
Table 1. Characteristics of the cohort at diagnosis (*n*=133)

Characteristic		
Age median (range)	8.1	(0.1-17.7)
	n	**(%)**
Gender: female	70	(52.6)
Diagnosis:		
Hematological	53	(39.8)
Leukemia	39	(29.3)
ALL	31	(23.3)
AML	8	(6.0)
Lymphoma	14	(10.5)
Solid tumors	44	(33.1)
Neuroblastoma	12	(9.0)
Wilms tumors	6	(4.5)
Bone	9	(6.8)
Solid other	17	(12.8)
Brain tumors	36	(27.1)
Medullo- and ependymoblastoma	8	(6.0)
Astrocytoma/glioma	13	(9.8)
Craniopharyngioma	4	(3.0)
Other	11	(8.3)
(Naso) gastric tube feeding[a]	60	(45.1)
Intensity of Treatment Rating (ITR)		
No treatment	1	(0.8)
Least intensive	8	(6.0)
Moderate intensive	60	(45.1)
Very intensive	59	(44.4)
Most intensive	5	(3.8)
Cranial radiotherapy (brain malignancies n=36)	16	(44.4)
Corticosteroids[b] (%)	78	(58.6)

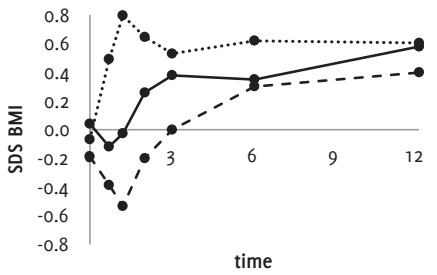
[a] Number of patients receiving gastric tube feeding at any given time during treatment. One patient had gastrostomic tube feeding, all the others received nasogastric tube feeding.
[b] Corticosteroid use according to treatment protocol or after brain surgery.



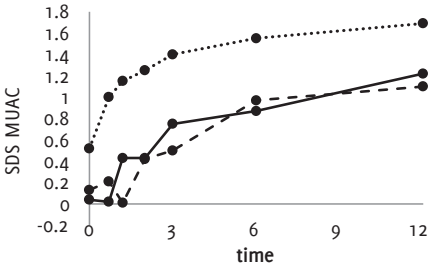
a. Change in WFA



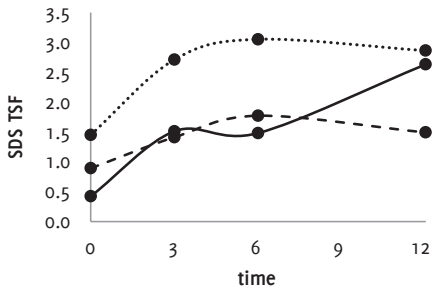
b. Change in HFA



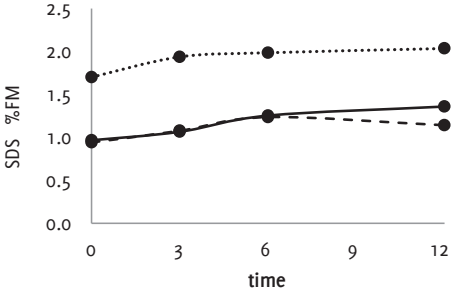
c. Change in BMI



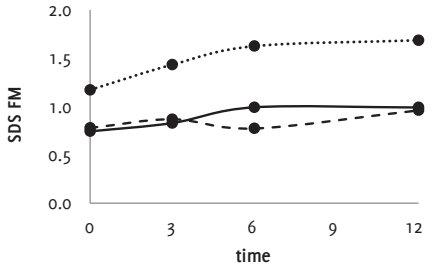
d. Change in MUAC



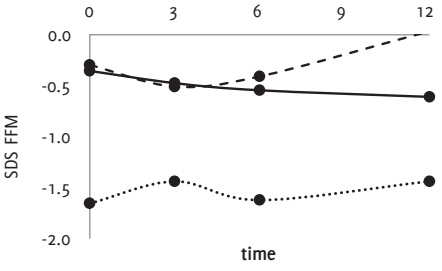
e. Change in TSF



f. Change in %FM



g. Change in FM



h. Change in FFM

Figure 2. Change in parameters of body size and body composition 0-12 months after diagnosis expressed in SDS. Data are presented of patients with hematological, solid, and brain malignancies. WFA (2a) and BMI (2c) initially decreased in patients with hematological and solid malignancies; whereas a rapid increase was observed in patients with brain malignancies. Within 3 months WFA and BMI were higher than at diagnosis in all malignancies, and the increase of BMI continued. HFA (2b) decreased in all patients groups, and MUAC (2d) increased. TSF (2e), %FM (2f), and FM (2g) increased and were higher in patients with brain malignancies compared to those with hematological and solid malignancies. FFM (2h) remained stable and was lower in patients with brain malignancies compared to patients with hematological and solid malignancies. FFM, fat free mass; FM, fat mass; HFA, height-for-age; MUAC, mid-upper arm circumference; SDS, standard deviation score; TSF, triceps skinfold thickness; WFA, weight-for-age.

—— hematological – – – – solid ·····brain malignancies

Table 2. Weight changes >5% in different time periods.

	0-3 months[a]			3-12 months[b]		
Patientgroups	Loss *n* (%)	Loss & gain *n* (%)	Gain *n* (%)	Loss *n* (%)	Loss & gain *n* (%)	Gain *n* (%)
All patients	17 (13.7)	18 (14.5)	44 (35.5)	1 (0.9)	13 (11.3)	70 (60.9)
Hematological	10 (19.6)	11 (21.6)	13 (25.5)	0	10 (20.8)	24 (50.0)
Solid	6 (14.3)	6 (14.3)	14 (33.3)	1 (2.6)	1 (2.6)	29 (74.4)
Brain	1 (3.2)	1 (3.2)	17 (54.8)	0	2 (7.1)	17 (60.7)

[a] In the period of 0-3 months, weight was assessed every 3 weeks, so the numbers refer to changes in a short period of time. Some patients lost weight in one period and gained weight in another period, and vice versa.
[b] In the period 3-12 months weight was assessed at 3, 6, and 12 months, so the numbers refer to changes in periods of 3 months and 6 months. Some patients lost weight in one period and gained weight in another period and vice versa.

of the brain tumor patients gained weight. The number of undernourished patients (BMI<-2SDS) decreased from 8.3% to 4.1% at 3 months, and the number of overnourished patients (BMI>2SDS) increased from 4.5% till 6.6% (Table 3).

On average, WFA increased and height-for-age (HFA) decreased (Figure 2a, 2b, table 4). As a result BMI (Figure 2c) increased on average with 0.13 SDS per month. Increase in weight was also reflected in increase of MUAC (Figure 2d, table 4).

3-12 months

During this period of less intensive treatment, no significant increase in WFA was found. HFA decreased with 0.02 SDS per month (Table 4), and both BMI

Table 3. Percentage under- and overnourished patients at different measurement times.[a]

	Undernourished				Overnourished			
	BMI<-2SDS	FFM<-2SDS		Total[c]	BMI>2SDS	FM>2SDS		Total[d]
Time		FM<2SDS	FM>2SDS[b]			FFM>-2SDS	FFM<-2SDS[b]	
0 months	8.3 (11/133)	16.1 (15/93)	1.1 (1/93)	18.9 (25/133)	4.5 (6/133)	9.8 (9/92)	1.1 (1/92)	8.3 (11/133)
3 months	4.1 (5/121)	14.8 (13/88)	2.2 (2/88)	15.7 (19/121)	6.6 (8/121)	11.4 (10/88)	2.2 (2/88)	12.4 (15/121)
6 months	1.8 (2/111)	13.6 (11/81)	1.2 (1/81)	11.7 (13/111)	9.9 (11/111)	14.8 (12/81)	1.2 (1/81)	15.3 (17/111)
12 months	1.7 (2/115)	13.6 (11/81)	3.7 (3/81)	14.0 (16/115)	10.4 (12/115)	14.8 (12/81)	3.7 (3/81)	18.3 (21/115)

[a] All values are percentages, with the number of under- or overnourished patients out of the total number patients between brackets. FFM, fat free mass; FM, fat mass; SDS, standard deviation score. Since FFM and FM could only be calculated for patients ≥ 4 years old, the total number of patients for FFM and FM is smaller than for BMI. Due to loss to follow-up, the number of patients differs between the measurement times.

[b] Four patients had both low FFM (<-2 SDS) and high FM (>2SDS) at the same time at one (n=3) or more (n=1) of the measurement times.

[c] Based on BMI < -2 SDS and/or FFM < -2 SDS.

[d] Based on BMI >2 SDS and/or FM > 2 SDS.

Table 4. Average changes in SDS per month in body size and body composition in three time periods.[a]

	0-3 months			3-12 months			0-12 months		
	Change	95% CI	*P* value	Change	95% CI	*P* value	Change	95% CI	*P* value
Body size									
WFA	0.06	0.03, 0.10	< 0.001	0.01	-0.00, 0.02	0.184	0.02	0.01, 0.03	0.001
HFA	-0.05	-0.07, -0.03	< 0.001	-0.02	-0.03, -0.01	0.001	-0.02	-0.03, -0.02	< 0.001
BMI	0.13	0.08, 0.18	< 0.001	0.02	0.00, 0.04	0.013	0.04	0.03, 0.06	< 0.001
MUAC	0.21	0.15, 0.27	< 0.001	0.05	0.02, 0.07	0.001	0.08	0.06, 0.10	< 0.001
Body composition									
TSF	0.33	0.22, 0.45	< 0.001	0.07	0.02, 0.12	0.006	0.12	0.08, 0.18	< 0.001
%FM	0.06	-0.00, 0.11	0.052	0.02	-0.00, 0.04	0.106	0.03	0.01, 0.05	0.001
FM	0.05	0.01, 0.10	0.021	0.02	-0.02, 0.05	0.400	0.02	0.01, 0.04	0.003
FFM	-0.01	-0.7, 0.05	0.802	-0.00	-0.03, 0.02	0.772	-0.00	-0.02, 0.01	0.622

[a] The average changes in SDS per month were calculated using multilevel analyses. Details are presented in the supplement tables 1-3. HFA, height-for-age; FFM, fat free mass; FM, fat mass; MUAC, mid-upper arm circumference; SDS, standard deviation score; TSF, triceps skinfold thickness; WFA, weight-for-age.

and MUAC gradually increased (Table 4, figure 2c and 2d). The magnitude of increases in BMI and MUAC and decreases in HFA did not differ between the three patient groups (Supplementary table 2). Prevalence rates of overnutrition doubled from the time of diagnosis to 10.4% at the end of the year, and the prevalence of undernutrition decreased to 1.7% (Table 3).

Despite the average increase in BMI, 12.2% (n=14) of the patients, in particular hematological patients, experienced >5% weight loss at any given time during this study period (Table 2).

Changes in body composition

0-3 months

At diagnosis, 17.2% (n=16) of the patients were undernourished according to FFM<-2SDS and this number remained stable during this period (Table 3). More than half of these patients (n=10) had normal BMI values and were diagnosed with brain malignancies (n=8). Based on FM>2SDS, 10.9% (n=10) were overnourished. However, half of the patients (n=5) with FM>2SDS had values of BMI<2SDS.

Body composition changed significantly: TSF and FM increased with 0.33 and 0.05 SDS per month respectively (Table 4, figure 2e, 2g); whereas FFM remained low (Figure 2h). Body composition also differed between the patient groups: patients with brain malignancies had higher FM and lower FFM compared with patients with hematological and solid malignancies (Supplementary table 1).

3-12 months

Changes in body composition continued during this period (Figures 2e-2h). However, only increase in TSF proved to be significant (Table 4). Although FFM in solid malignancy patients seemed to increase (Figure 2h), the change was not significant. The differences in body composition between the groups remained; higher FM and lower FFM were found in patients with brain malignancies (Supplementary table 2). One year after diagnosis, 18.5% (n=15) of the patients had FM>2SDS; these were mainly patients with ALL, lymphoma, and craniopharyngioma. Another 17.3% (n=14) had FFM<-2SDS, including all malignancies. Some patients (n=4) had low FFM (FFM<-2SDS) and high FM (FM>2SDS) at the same time. Three of these 4 patients were diagnosed with brain malignancies (craniopharyngioma). Mean FFM SDS in patients with BMI<-2 SDS was 1.09 SDS (%CI -1.68; -0.51, P=0.000) lower than in the overnourished patients (BMI> 2SDS).

Factors related to changes in BMI

0-3 months

The increase in BMI during this period was related to initial nutritional status and tube feeding. The BMI of children with a lower nutritional status at diagnosis and the BMI of children who received tube feeding increased more (estimate of slope interaction nutritional status*time= -0.07, 95%CI -0.10; -0.03, P=0.000; estimate of slope interaction tube feeding*time=-0.13 per month, 95%CI -0.25; -0.00, P=0.047, Supplementary Table 4). Although the three diagnosis groups (hematological, solid, and brain malignancies) did not differ in the extent of increase in BMI, the trajectories of the three groups were different. For example, the BMI of both the hematological malignancies group and the solid malignancies group first decreased, only to recover within 3 months. In contrast, the BMI of the brain malignancies group increased immediately after diagnosis. Furthermore, in this period older children had relatively lower BMI (estimate of intercept -0.04, 95%CI -0.06; -0.01, P=0.008), and patients with solid malignancies had relatively lower BMI than patients with brain malignancies (estimate of intercept -0.53, 95%CI -0.97; -0.10, P=.0016).

3-12 months

No single factor appeared to be related to the increase in BMI. Hence, an increase in BMI between 3-12 months was not related to age, gender, diagnosis, BMI parents, initial nutritional status, energy intake, tube feeding, treatment intensity or phase, corticosteroids, symptoms, or activity.

Factors related to increase in %FM

0-12 months

The only factor related to increase in %FM was the Lansky PPS. The %FM of severely ill and less active children was found to increase more (estimate of slope interaction Lansky*time -0.001, 95%CI -0.002; -0.0002, P=0.018) (Supplementary table 5). Every single point decrease in PPS (scale 10-100) resulted in a 0.001 increase in %FM per month, indicating that a decrease of 20 points in PPS-score contributed to an increase of 0.24 SDS in %FM over 12 months. The increase in %FM was not related to age, gender, diagnosis, BMI parents, initial nutritional status, energy intake, tube feeding, treatment intensity or phase, corticosteroids, or symptoms. Furthermore, patients with brain malignancies had higher %FM than patients with hematological (estimate of intercept -0.74, 95%CI -1.12; -0.36, P=0.000) and solid

malignancies (estimate of intercept -0.89, 95%CI -1.30; -0.47, P=0.000), and patients with tube feeding had higher %FM than patients without tube feeding (estimate intercept -0.28, 95%CI -0.54; -0.03, P=0.028).
An additional Kruskal Wallis analysis was performed to investigate the impact of corticosteroid doses on increase in %FM in 3 ALL risk groups. These risk groups, receiving different doses of corticosteroids, did not differ with regard to increase in %FM (H= 0.359, df=2, P=0.836).

DISCUSSION

This is the first study to describe the trajectories of changes in nutritional status during treatment of children with hematological, solid and brain malignancies. The greatest changes occurred within 3 months after diagnosis. Tube feeding and diminished activity level were identified as the significant contributory factors to increases in BMI and %FM respectively.

Changes in body size

In our study, increase in BMI in patients with brain malignancies started immediately after diagnosis; whereas BMI in patients with hematological and solid malignancies initially decreased, only to increase later on. In contrast, other studies reported increase in BMI from the start of treatment, particularly in patients with ALL[18,19] and craniopharyngioma.[20] However, data in those studies were collected retrospectively, and, in general, time intervals of 6 months or more were used. Thus, presentation of changes was less precise and detailed compared with the current study. In our study, for example, the BMI of patients with solid malignancies did not show the continuous decrease that has been observed elsewhere,[21] but instead recovered within three months. Obviously, variation in nutrition policies and interventions affected the BMI trajectories in the different studies. Since all patient groups in the current study were treated according to the same nutrition policy, (nutritional assessment, a personal dietary advice from a dietician, and regular measurement of weight and height), we were in the unique position to analyze the impact of the type of malignancy on nutritional status.
Furthermore, we found that stagnation of growth in height contributed to increase in BMI. Consequently, it is important for clinicians to realize that in order to prevent increase in BMI during treatment weight should remain

stable until growth in height continues.
Our study results indicate that despite initial weight loss in patients with hematological and solid malignancies, eventually all three patient groups were at risk for becoming overnourished. Since higher prevalence rates of overnutrition have also been found in childhood cancer survivors,[20,22] a timely identification of changes in BMI during treatment is necessary to implement preventive measures.

Changes in body composition

Our finding of rapid increase in FM during the first months after diagnosis is consistent with findings in ALL patients.[9] Due to the small time intervals we could determine the period of rapid increase more precisely. We found that childhood cancer patients start gaining FM almost immediately after diagnosis and during the most intensive period of treatment. There is a paucity of data on changes of body composition in children with solid or brain malignancies.[7] Both high[6] and stable FM have been reported in solid malignancy patients.[23] In the current study, all patient groups were found to be at risk for increase in FM. This increase in FM during treatment is of serious concern, particularly since the literature reports increased levels of FM even years after cessation of therapy in survivors of childhood cancer.[24,25] This indicates that high FM developed during treatment might continue into survivorship and increase the risk of morbidities associated with overnutrition.
FFM was already low at diagnosis and remained low during treatment, with the lowest values found in patients with brain malignancies. Low FFM, at diagnosis and during treatment, has been reported before in ALL and solid malignancy patients[6,9] and might be caused by weight loss or inflammation due to tumor activity. The abnormal body composition in patients with brain malignancies could be attributed to a growth hormone deficiency that was already present at diagnosis[26] or to diminished physical activity due to motor disabilities. Some patients, especially patients with craniopharyngioma, had low FFM and high FM at the same time. Since overnutrition is more visible than undernutrition, the undernourishment of these patients often goes undetected. Low FFM is alarming because it results in loss of muscle strength, lower tolerance for chemotherapy, higher risk of infections, and poorer outcomes.[6] Low FFM might even continue after cessation of therapy as was demonstrated in survivors.[25] Therefore, further research on the onset and factors related to low FFM is urgently needed.
A limitation of the current study is that only simple methods were used to

assess body composition. The accuracy and precision of BIA can be influenced by intrapersonal factors such as illness and hydration status. In addition, a disease specific equation for predicting FFM in childhood cancer patients using BIA measurements is not yet available. Triceps measurement can also be prone to measurement bias, especially in overnourished persons. However, these methods are not only fast and easy to use, but they are also acceptable to children. Moreover, the presentation of TSF as SDS is considered to be a reliable index for FM.[27] By performing the measurements between courses of chemotherapy, in the absence of fever, hyper-hydration, and edema and by application of both BIA and TSF; we have tried to optimize the validity of the body composition assessment. Furthermore, the FM results of BIA and TSF were closely related and followed similar trajectories.

Factors related to increase in BMI

Low initial nutritional status and tube feeding contributed to an increase in BMI. The faster increase in BMI in poorly nourished children at the time of diagnosis might be seen as catch-up growth. Tube feeding also contributed to weight gain in this particular group of children. However, it is difficult to draw the line between catch-up growth and overfeeding. The high percentage (45%) of patients receiving tube feeding combined with the high energy intake in the early phase of treatment not only reveals an active policy to prevent and treat undernutrition but also explains the rapid recovery of BMI after decline. Nevertheless, the continuous increase in BMI indicates that the average energy intake of patients exceeded their energy requirements. This suggests that concern about weight loss has conversely resulted in neglect of weight gain.

Contrary to other studies, we did not find an association between increase in BMI and age, gender, or parental BMI,[18,19,28] nor did we find an association with energy intake, treatment intensity, symptoms, or physical activity. All these factors were interrelated to tube feeding, making tube feeding the main related factor for weight gain. Considering these interrelationships, the need for tube feeding can be seen as a surrogate marker of children who are severely affected by the disease and treatment. However, despite the severity of their disease, BMI in these children continued to increased due to the forced tube feeding. Treatment with corticosteroids is often linked to increase in BMI, since energy intake increases during corticosteroid treatment.[29,30] However, studies testing the impact of corticosteroids on BMI have shown contradictory results.[19,31] In our study, an association with corticosteroid use was not found.

Factors related to increase in %FM

Low physical activity (Lansky PPS) was found to be the main factor contributing to increase in %FM. This finding is congruent with research in healthy children and adolescents.[32] Similar to increase in BMI, high energy intake or treatment with corticosteroids are assumed to cause increase in FM.[6,9,23] Again, similar to the BMI results, such a relationship was not found. The results of the current study demonstrated that the level of activity was the only contributing factor to increase in %FM. Physical activity is known to be lower during cancer treatment,[33] especially during treatment periods with corticosteroids.[30] Due to this low level of activity, it can be concluded that increase in weight was due to increase in FM.

This study is one of the very few prospective cohort studies describing the changes in nutritional status in patients with heterogeneous malignancies. Although the sample size of the separate malignancies was small, the longitudinal study design and low drop-out rate make the results of this study useful for developing nutritional strategies to improve outcomes in children with cancer.

The current findings have several clinical implications. First, the fact that childhood cancer patients had abnormal body composition stresses the importance of not only assessing weight and height, but of FFM and FM as well. By only considering weight and height, some malnourished or obese children may remain unrecognized. This is particularly true for patients with brain malignancies. Since low FFM is associated with poorer prognoses[6], regular measurement of body composition, for instance using BIA, is urgently recommended. Second, given the low FFM and diminished physical activity, protein needs during treatment might be increased.[34] Therefore, nutritional interventions aimed at treating or preventing undernutrition should meet these protein demands while energy intake should match patients' energy requirements. In order to prevent overfeeding, nutritional status should be monitored more carefully. BMI growth charts could play a pivotal role here. Furthermore, in order to reduce FM and to increase FFM, clinicians should begin to focus on strategies to improve physical activity from the start of treatment.

In conclusion, our findings show that significant increases in BMI and %FM already occurred within the first 3 months after diagnosis and eventually resulted in a doubling of the percentages of obese patients after 12 months. Nevertheless, some children did experience weight loss, and 17% were

malnourished according to low FFM. Improvement of nutritional status might be accomplished by adequate dietary intake and increased physical activity as to prevent energy imbalances and to improve FFM. Such measures will eventually contribute to better outcomes.

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SUPPLEMENT

Items of the two subscales derived from MSAS
Scale feeding related symptoms
Pain
Lack of energy
Cough
Dry mouth
Nausea
Vomiting
Shortness of breath
Diarrhea
Lack of appetite
Difficulty swallowing
Mouth sores
Change in the way food tastes
Constipation

Scale nausea and vomiting
Nausea
Vomiting

Supplementary table 1.
Change in SDS per month in body size and body composition in the period of **0-3 months** based on multilevel analyses. Unconditional growth models and best models (based on likelihood ratio test) with diagnosis as covariate are presented.

		Estimate	95%CI	P value	Estimate	95%CI	P value
Body size		**Unconditional growth model**			**Conditional growth model**		
WFA							
Intercept		-0.02	-0.24, 0.20	0.851	0.06	-0.37, 0.48	0.788
Time		**0.06**	0.03, 0.10	0.000	0.14	0.07, 0.21	0.000
Diagnosis	Hematological				-0.07	-0.62, 0.48	0.788
	Solid				-0.15	-0.72, 0.42	0.609
	Brain				0		
Diagnosis*time	Hematological				-0.08	-0.16, 0.00	0.057
	Solid				-0.12	-0.21, -0.03	0.006
	Brain				0		
HFA							
Intercept		0.09	-0.12, 0.31	0.402			
Time		-0.05	-0.07, -0.03	0.000			
BMI							
Intercept		-0.11	-0.35, 0.12	0.342	0.22	-0.21, 0.64	0.316
Time		**0.13**	0.08, 0.18	0.000	0.13	0.08, 0.18	0.000
Diagnosis	Hematological				-0.26	-0.79, 0.27	0.342
	Solid				-0.68	-1.24, -0.13	0.016
	Brain				0		
MUAC							
Intercept		0.19	-0.12, 0.50	0.222	0.78	0.23, 1.33	0.006
Time		**0.21**	0.15, 0.27	0.000	0.21	0.15, 0.27	0.000
Diagnosis	Hematological				-0.74	-1.44, -0.05	0.037
	Solid				-0.87	-1.60, -0.15	0.019
	Brain						

Body composition							
TSF							
Intercept		0.74	0.35, 1.14	0.000	1.48	.71, 2.25	0.000
Time		**0.33**	0.22, 0.45	0.000	0.34	0.22, 0.45	0.000
Diagnosis	Hematological				-1.08	-2.04, -0.12	0.028
	Solid				-0.81	-1.83, 0.20	0.115
	Brain				0		
%FM							
Intercept		1.14	0.93, 1.35	0.000	1.74	1.36, 2.11	0.000
Time		**0.06**	-0.0005, 0.11	0.052	0.06	-0.0002, 0.11	0.051
Diagnosis	Hematological				-0.78	-1.24, -0.32	0.001
	Solid				-0.82	-1.31, -0.33	0.001
	Brain				0		
FM							
Intercept		0.85	0.66, 1.04	0.000	1.25	0.91, 1.59	0.000
Time		**0.05**	0.01, 0.10	0.021	0.05	0.01, 0.10	0.020
Diagnosis	Hematological				-0.54	-0.96, -0.11	0.013
	Solid				-0.55	-1.00, -0.10	0.018
	Brain				0		
FFM							
Intercept		-0.67	-0.96, -0.38	0.000	-1.46	-1.97, -0.95	0.000
Time		**-0.01**	-0.07, 0.05	0.802	-0.01	-0.07, 0.05	0.784
Diagnosis	Hematological				1.05	0.42, 1.67	0.001
	Solid				1.06	0.39, 1.73	0.002
	Brain				0		

HFA, height-for-age; FFM, fat free mass; FM, fat mass; MUAC, mid-upper arm circumference; SDS, standard deviation score; TSF, triceps skinfold thickness; WFA, weight-for age.

Supplementary table 2. Change in SDS per month in body size and body composition in the period of **3-12 months** based on multi- level analyses. Unconditional growth models and best models (based on likelihood ratio test) with diagnosis as covariate are presented.

		Estimate	95%CI	*P* value	Estimate	95%CI	*P* value
Body size		**Unconditional growth model**			**Conditional growth model**		
WFA							
Intercept		0.16	-0.04, 0.37	0.118			
Time		**0.01**	-0.004, 0.02	0.184			
HFA							
Intercept		0.01	-0.22, 0.25	0.905			
Time		**-0.02**	-0.03, -0.01	0.001			
BMI							
Intercept		0.24	0.02, 0.47	0.034			
Time		**0.02**	0.004, 0.04	0.013			
MUAC							
Intercept		0.72	0.40, 1.04	0.000			
Time		**0.05**	0.02, 0.07	0.001			
Body composition							
TSF							
Intercept		1.43	0.89, 1.97	0000	2.34	1.38, 3.30	0.000
Time		**0.07**	0.02, 0.12	0.006	0.07	0.02, 0.12	0.006
Diagnosis	Hematological				-1.15	-2.29, -0.01	0.048
	Solid				-1.24	-2.46, -0.03	0.045
	Brain				0		
%FM							
Intercept		1.27	1.02, 1.53	0.000	1.92	1.53, 2.32	0.000
Time		**0.02**	-0.004, 0.04	0.106	0.02	-0.003, 0.04	0.086
Diagnosis	Hematological				-0.80	-1.24, -0.35	0.001
	Solid				-0.96	-1.44, -0.49	0.000
	Brain				0		
FM							
Intercept		0.95	0.72, 1.18	0.000	1.40	0.96, 1.84	0.000
Time		**0.02**	-0.02, 0.05	0.400	0.02	-0.02, 0.05	0.424
Diagnosis	Hematological				-0.56	-1.10, -0.01	0.046
	Solid				-0.65	-1.24, -0.05	0.034
	Brain				0		
FFM							
Intercept		-0.68	-0.98, -0.37	0.000	-1.49	-2.02, -0.96	0.000
Time		**-0.00**	-0.03, 0.02	0.772	-0.00	-0.03, 0.02	0.760
Diagnosis	Hematological				0.95	0.31, 1.59	0.004
	Solid				1.26	0.57, 1.95	0.000
	Brain				0		

HFA, height-for-age; FFM, fat free mass; FM, fat mass; MUAC, mid-upper arm circumference; SDS, standard deviation score; TSF, triceps skinfold thickness; WFA, weight-for age.

Supplementary table 3. Change in SDS per month in body size and body composition in the period of **0-12 months** based on multi- level analyses. Unconditional growth models and best models (based on likelihood ratio test) with diagnosis as covariate are presented.

		Estimate	95%CI	*P* value	Estimate	95%CI	*P* value
Body size		**Unconditional growth model**			**Conditional growth model**		
WFA							
Intercept		0.05	-0.16, 0.25	0.655			
Time		**0.02**	0.01, 0.03	0.001			
HFA							
Intercept		0.06	-0.16, 0.28	0.572			
Time		**-0.02**	-0.03, -0.02	0.000			
BMI							
Intercept		0.06	-0.15, 0.26	0.569			
Time		**0.04**	0.03, 0.06	0.000			
MUAC							
Intercept		0.39	0.11, 0.68	0.008			
Time		**0.08**	0.06, 0.10	0.000			
Body composition							
TSF							
Intercept		0.97	0.57, 1.37	0.000	1.85	1.05, 2.65	0.000
Time		**0.12**	0.08, 0.18	0.000	0.12	0.08, 0.16	0.000
Diagnosis	Hematological				-1.24	-2.23, -0.25	0.015
	Solid				-1.04	-2.08, 0.01	0.052
	Brain				0		
%FM							
Intercept		1.19	0.99, 1.40	0.000	1.83	1.48, 2.18	0.000
Time		**0.03**	0.01, 0.05	0.001	0.03	0.01, 0.05	0.001
Diagnosis	Hematological				-0.79	-1.21, -0.37	0.000
	Solid				-0.93	-1.38, -0.48	0.000
	Brain				0		
FM							
Intercept		0.89	0.70, 1.08	0.000	1.33	0.99, 1.68	0.000
Time		**0.02**	0.01, 0.04	0.003	0.02	0.01, 0.04	0.002
Diagnosis	Hematological				-0.56	-0.99, -0.14	0.010
	Solid				-0.63	-1.08, -0.18	0.007
	Brain				0		
FFM							
Intercept		-0.67	-0.95, -0.39	0.000	-1.52	-2.01, -1.02	0.000
Time		**-0.00**	-0.02, 0.01	0.622	-0.01	-0.02, 0.01	0.588
Diagnosis	Hematological				1.03	0.41, 1.65	0.001
	Solid				1.27	0.61, 1.92	0.000
	Brain				0		

HFA, height-for-age; FFM, fat free mass; FM, fat mass; MUAC, mid-upper arm circumference; SDS, standard deviation score; TSF, triceps skinfold thickness; WFA, weight-for age.

Supplementary table 4. Associations between daily increases in BMI SDS in the period 0-3 months using multilevel analysis

		Change BMI SDS 0-3 months		
		Estimate	95% CI	P value
Intercept		0.63	0.21, 1.06	0.004
Time		0.30	0.11, 0.49	0.002
Time^2		-0.10	-0.21, -0.00	0.045
Age		-0.04	-0.06, -0.01	0.008
Diagnosis	Hematological	-0.06	-0.48, 0.35	0.766
	Solid	-0.53	-0.96, -0.10	0.016
	Brain	0		
Nutritional status Dx		0.51	0.43, 0.59	0.000
Tube feeding	No	0.08	-0.12, 0.29	0.416
	Yes	0		
Age*time		0.00	-0.01, 0.02	0.377
Diagnosis*time	Hematological	0.05	-0.13, 0.24	0.563
	Solid	-0.12	-0.30, 0.06	0.187
	Brain	0		
Nutritional statusDx*time		-0.07	-0.10, -0.03	0.000
Tube feeding*time	No	-0.13	-0.25, -0.00	0.047
	Yes	0		
Diagnosis*time^2	Hematological	0.20	0.07, 0.33	0.004
	Solid	0.14	0.01, 0.27	0.039
	Brain	0		

Dependent variable: BMI SDS, time is centered. Both time and time^2 are in the model and present the shape of a parabolic curve: the negative value of the estimate for the coefficient of time^2 means that the parabolic curve is concave (opening down) for the reference group (in this analysis the tube fed patient with brain malignancy). Nutritional statusDx (=initial nutritional status) is related to increase in BMI: a difference of 1 SDS higher nutritional status at diagnosis results in 0.07 less increase per day. Tube feeding is related to increase in BMI as well: children without tube feeding increase 0.13 SDS less in BMI compared with children with tube feeding. Diagnosis*time^2: the parabolic curves of patients with hematological and solid malignancies differ from patients with brain malignancies. Their parabolic curves are convex, meaning that BMI first decreased and subsequently increased (Figure 1a). Explained total variance of this model is 52.2%.

Supplementary table 5. Associations between monthly increases in %FM SDS by using multilevel analysis in the period of 0-12 months

		Change %FM 0-12 months		
		Estimate	**95% CI**	**P value**
Intercept		1.99	1.45, 2.54	0.000
Time		0.14	0.06, 0.22	0.001
Nutritional status Dx		0.38	0.26, 0.49	0.000
Diagnosis	Hematological	-0.74	-1.12, -0.36	0.000
	Solid	-0.89	-1.30, -0.47	0.000
	Brain	0		
Tube feeding	No	-0.28	-0.54, -0.03	0.028
	Yes	0		
Lansky		0.0003	-0.006, 0.007	0.929
Lansky*time		-0.001	-0.002, -0.0002	0.018

Dependent variable %FM SDS. Lansky is associated with increase in %FM over time: with every 1 point decrease in Lansky, %FM increases with 0.001 per month. Explained total variance of this model is 27.2%.

CHAPTER

5

FINDING THE RIGHT BALANCE: AN EVALUATION OF THE ADEQUACY OF ENERGY AND PROTEIN INTAKE IN CHILDHOOD CANCER PATIENTS

Aeltsje Brinksma
Petrie F. Roodbol
Esther Sulkers
Eveline S.J.M. de Bont
Johannes G.M. Burgerhof
Rienk Y.J. Tamminga
Harriët Jager-Wittenaar
Wim J.E. Tissing

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ABSTRACT

Background & aims: Despite a widespread belief that adequate dietary intake is needed to maintain weight during childhood cancer treatment, conclusive data about adequacy of intake are lacking. Therefore, we aimed to assess the adequacy of energy and protein intake in a heterogeneous childhood cancer population against 3 different norms.

Methods: We conducted a prospective cohort study of 115 children diagnosed with cancer and assessed dietary intake after diagnosis and at 3, 6, and 12 months. Intake was assessed against recommended daily allowances (RDA), intake in healthy controls, and calculated individual requirements; and subsequently related to changes in nutritional status.

Results: Energy intake was lower than RDA and lower than in healthy controls at all measurement points; whereas energy intake matched individual requirements at 2 of the 4 measurement points. Protein intake in childhood cancer patients was lower than in healthy children. However, protein intake was almost twice the RDA and one and a half times the individual requirements. During the study period, weight and fat mass (FM) increased significantly while fat free mass (FFM) remained low. Energy intake was negatively associated with weight and FM, and protein intake was not associated with FFM.

Conclusions: The patients' weight increased; whereas their energy intake was lower than RDA and lower than in healthy controls. This indicates that the average intake was more than adequate. Percentage intake of individual requirements matched with increased weight. Therefore, the use of this norm is preferable to RDA or intake in healthy controls when determining the adequacy of dietary intake in both clinical practice and futures studies.

INTRODUCTION

During childhood, adequate energy and protein intake is of the utmost importance, since this phase of life is characterized by rapid growth and development. In children with cancer adequate intake is even more important, particularly because inadequate dietary intake increases both morbidity and mortality and impedes normal growth and development.[1-3]

Our literature search[4] on intake in childhood cancer patients revealed that it was difficult to draw uniform conclusions about the adequacy of dietary intake because intake was assessed at different time points and because different norms were used. In some studies, for instance, energy intake was assessed against recommended dietary allowances (RDA) whereas other studies used energy intake in healthy controls as a norm. Furthermore, since none of these studies tested the impact of energy intake on nutritional status, it remains unknown whether inadequate energy intake according to requirements of RDA or intake in healthy controls resulted in weight loss or undernutrition. Only one cross-sectional study assessed energy intake against calculated individual requirements. This study reported worse nutritional status in the group with the lowest intake.[5]

It is questionable, however, whether RDA or intake in healthy controls are suitable norms to estimate energy requirements in children treated for cancer. An individual norm that includes specific patient characteristics might be a better alternative than group norms. In general, it is thought that energy requirements in cancer patients are elevated because of an increased metabolic rate due to tumor activity.[6] Therefore, it is recommended to increase energy intake in childhood cancer patients with 15-50% to compensate for this increased metabolic rate and for undernutrition.[7] However, the evidence for an increased metabolic rate in childhood cancer patients is inconclusive.[4] Moreover, since cancer patients are less active than healthy persons, increased energy needs for metabolic rate are often compensated by decreased needs for physical activity[8] Therefore, the ESPEN guidelines on nutrition in adult oncology patients state that "energy requirements in cancer patients should be assumed to be normal unless there are specific data showing otherwise" (p. 447).[9]

In contrast to the literature on energy intake, literature on protein requirements during childhood is scarce. Proteins are essential for growth and synthesis of lean body mass. During illness, protein requirements are assumed to be increased to compensate for muscle wasting which is caused by inflammation

and inactivity.[10] Nevertheless, evidence for increased protein needs in children is scarce.[11]
In view of the lack of conclusive data regarding the adequacy of dietary intake in children treated for cancer, we conducted a prospective cohort study and assessed adequacy of dietary intake against three different norms: calculated individual requirements, RDA, and intake in healthy controls. Dietary intake was measured at 4 time points: after diagnosis and at 3, 6, and 12 months. Our research questions were: 1) How are these three norms interrelated? 2) How are these norms related to changes in nutritional status?

METHODS

Participants

In the period between September 2007 and December 2009, all children between 0-18 years of age who were consecutively admitted to the Pediatric Oncology Department of the University Medical Center Groningen (UMCG) and who were newly diagnosed with cancer were approached for the Pecannut (Pediatric Cancer and Nutrition) study. Exclusion criteria were: being unable to understand the Dutch language or receiving non-curative treatment. In total, 150 patients were eligible for inclusion. Twenty patients refused participation because they found the study too burdensome (n=17) or because they experienced a lack of motivation (n=3) (response rate 87%). After inclusion 15 patients left the study because they became too ill or died (n=3), experienced too much burden (n=5), experienced a lack of motivation (n=5), or experienced language difficulties with the questionnaires (n=2). Finally, 115 patients participated in the study. Ethical approval was obtained from the Medical Ethics Committee of the UMCG, and both parents and children aged ≥ 12 years gave their written consent.

Measures

Dietary intake data were collected using 3-day food records (3 consecutive days, including 1 weekend day) within the first 1-3 weeks after diagnosis and at 3, 6, and 12 months. This method has been shown to be an accurate and valid method for assessment of dietary intake.[12] In addition to the amount of intake, it was registered whether the child received solely oral feeding or tube feeding (with or without additional oral feeding). Furthermore, data on

vomiting and diarrhea were registered as well.
Weight was measured using a calibrated digital scale and recorded to the nearest 0.1 kg (for infants to the nearest 0.01 kg). During measurements children only wore underwear. Height was measured using a calibrated digital stadiometer or an infantometer for infants, and recorded to the nearest 0.1 cm. To adjust for age and gender, standard deviation scores (SDS) of weight, height, and weight-for-height (WFH) were calculated according to Dutch reference standards.[13] Undernutrition was defined as WFH< -2 SDS and overnutrition as WFH> 2 SDS. Body composition was determined by bioelectrical impedance analyses (BIA) using a 50 kHz frequency BIA (BIA 101, Akern, Italy). After calculating fat free mass (FFM) with the equation of Goran,[14] fat mass (FM) and percentage fat mass (%FM) were calculated and expressed as SDS using Dutch reference values.[15] All measurements were taken after diagnosis and at 3, 6, and 12 months. The follow-up measurements were taken between courses of chemotherapy and in the absence of fever, intravenous hyperhydration, and edema.

Data analysis and statistics

Dietary intake of energy and protein was calculated using food calculation software (Eetmeter 2002, The Netherlands Nutrition Centre, The Netherlands). Data on vomiting and diarrhea were incomplete and therefore not included in the analysis. Individual energy requirements (EIR_c) were calculated with the prediction formula recommended by the Dutch Malnutrition Steering Group[16] and included metabolic rate (RMR) (calculated using Schofield's equations[17]), physical activity (PAL), growth (GF), and energy absorption coefficient (EAC) (for further details see Supplementary tables).

$$EIR_c = RMR \times PAL \times GF / EAC$$

The illness factor was omitted from the equation since the evidence for increased energy requirements due to an increased metabolic rate is inconclusive.[4] Furthermore, the first assessment of intake took place after the start of treatment, and in this particular patient group increased metabolic rate has never been demonstrated after the start of treatment. The PAL was based on Lansky Play Performance scale[18] and ranged from 1.0-1.5 depending on the activity level of the child (Supplementary table 2); GF ranged from 1.02 to 1.3 depending on the age of the child (Supplementary table 3), and EAC

was age dependent as well and ranged from 0.60-0.98 (Supplementary table 4). Subsequently, percentage energy intake of individual requirement (%EIR_c = measured energy intake / EIR x 100) was calculated. Individual protein requirements (PIR_c) were calculated by multiplying the child's weight with the recommended protein intake of the Dutch Malnutrition Steering Group[19] (Supplementary table 5). In addition, percentage protein intake of individual requirement was calculated (%PIR_c).

Data on RDA were derived from the recommendations of the Health Council of the Netherlands[20] (Supplementary table 6). Data on intake of healthy children were derived from the Dutch National Food Consumption Survey Young Children 2005/2006 (FCS)[21] and from the Dutch National Food Consumption Survey 2007-2010[22] (Supplementary table 7). In these surveys, no data were available on healthy children younger than 2 years.

Daily intake of energy and protein was compared to individual requirements. Energy intake was defined as adequate if $90 \leq \%EIR_c \leq 110$. Adequacy of protein intake was age dependent and was defined as adequate if between: 1.8 -2.5 g/kg/day for children 0-2 months; 1.4-2.5 g/kg/day for children 3-5 months; 1.2-2.5 g/kg/day for children 6-11 months; and 1.2-2.0 g/kg/day for children 1-18 year [19,23]

Subsequently, energy and protein intake of each child was compared to the age and gender corresponding values of RDA and the age and gender corresponding data of healthy children as assessed in the FCS. For this purpose, paired t-tests were used or sign-tests if assumptions for normal distribution of differences were not met.

Moreover, percentage intake of RDA and FCS was calculated. Differences between energy and protein intake at the 4 measurement points were tested with ANOVA in linear mixed models using multilevel analyses. Furthermore, multilevel analyses were performed: (1) to determine whether intake changed over time; (2) to determine differences in intake between oral and tube fed children; (3) to determine whether %EIR was associated with weight, WFH, height, FM, %FM, and whether %PIR was associated with FFM. Likelihood ratio tests were used to determine the best multilevel solution. All cases, including cases with missing data, were included for analyses. Analyses were performed using IBM SPSS Statistics 20. Statistical significance was accepted at the 5% level.

RESULTS

Patient characteristics

In total, dietary intake data of 115 patients with hematological (47/115, 41%), solid (38/115, 33%) and brain (30/115, 26%) malignancies were available (Table 1). Dietary data of several patients were missing at one or more measurement points resulting in dietary data of 98 patients after diagnosis, 74 at 3 months, 73 at 6 months, and 70 at 12 months (Figure 1). After diagnosis, 29% (33/115) received additional or full nasogastric tube feeding. This percentage decreased to 14% (10/70) (McNemar χ^2=6.86, df=1, P=0.009) during the 12 months after diagnosis. In total, 44% (51/115) of the patients received tube feeding for several days or weeks at any given time during the 12 months period.

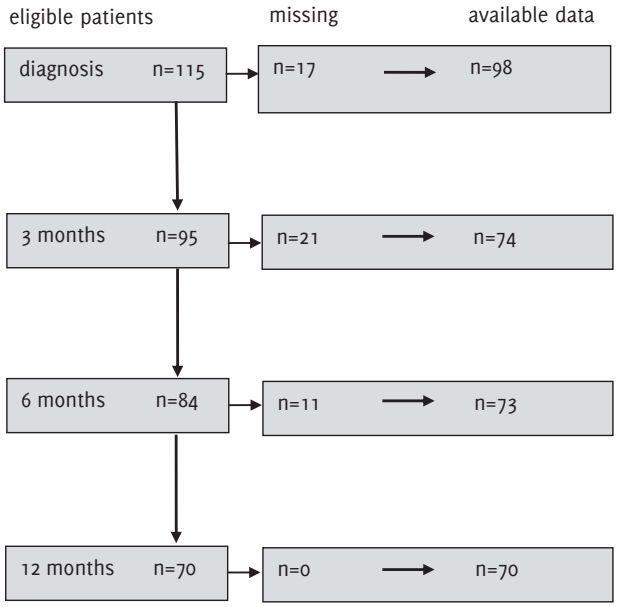


Figure 1. Flow chart of follow-up.
Reasons for loss to follow-up (n=45) were: child was too ill (n=9), died (n=5), moved (n=3), experienced too much burden (n=12), or lost motivation for participation (n=16).

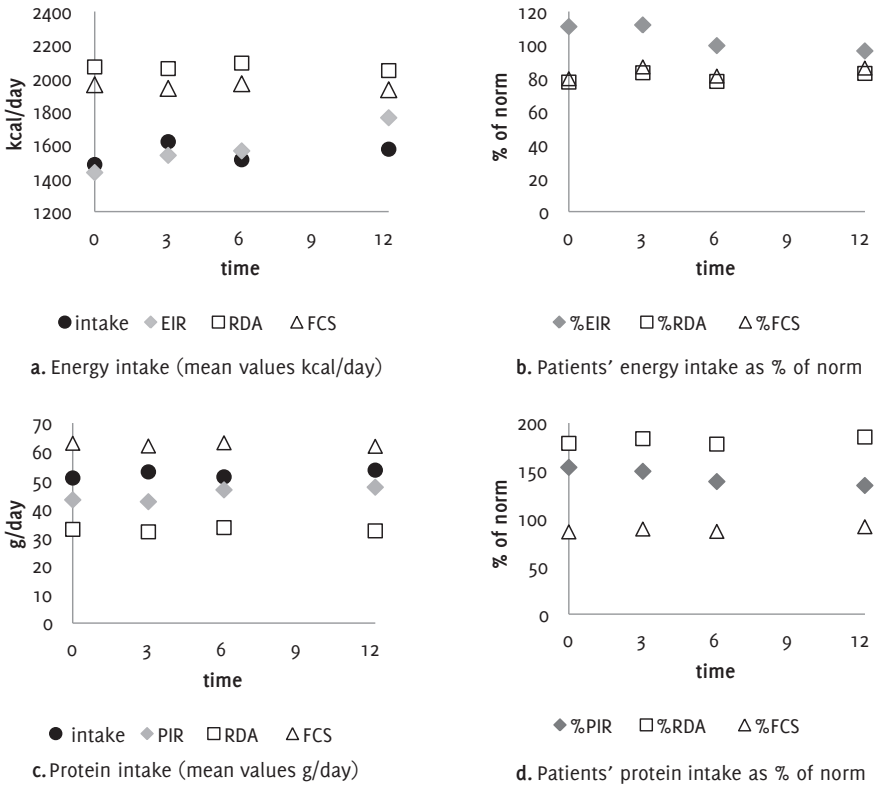
Table 1. Characteristics of the cohort at diagnosis (*n*=115)

Characteristic		
Age median (range)	8.1	(0.1-17.7)
	n	**(%)**
Gender: female	61	(53)
Diagnosis:		
Hematological	47	(41)
Leukemia	36	(31)
ALL	29	(25)
AML	7	(6)
Lymphoma	11	(10)
Solid tumors	38	(33)
Neuroblastoma	10	(9)
Wilms tumors	5	(4)
Bone	8	(7)
Solid other	15	(13)
Brain tumors	30	(26)
Medullo- and ependymoblastoma	6	(5)
Astrocytoma/glioma	10	(9)
Craniopharyngioma	4	(3)
Other	10	(9)
Nasogastric tube feeding[a]	51	(44)

[a] Number of patients receiving nasogastric tube feeding at any given time during treatment.

Energy intake

Mean energy intake of the patients was 1482 (SD 714) kcal/day after diagnosis and 1574 (SD 519) kcal/day after 12 months (Table 2). Energy intake expressed in kcal/day did not differ between the 4 measurement points (Multilevel ANOVA F=0.753, P=0.522). Patients' energy intake was higher compared to their individual requirements (EIR_c) at 3 months after (t=2.394, df=63, P = 0.020) and lower at 12 months (t =-2.058, df=62, P=0.044) (Figure 2a). After diagnosis and at 6 months energy intake matched the requirements (t= 0.330, df 84, P= 0.743; Z= .125, P= 0.901 respectively). Mean $\%EIR_c$ during the study period was 105% and decreased from 111% at the beginning of treatment to 96% after 12 months (estimate slope -1.46 per month, 95% CI -2.38; -.54, P=0.002) (Figure 2b). Compared to EIR_c, at the different time points energy intake of 16-41% was inadequate (<90% of EIR_c); 14-37% of the patients had an adequate intake (90-110% of EIR_c); and



a. Energy intake (mean values kcal/day)

b. Patients' energy intake as % of norm

c. Protein intake (mean values g/day)

d. Patients' protein intake as % of norm

Figure 2. Energy and protein intake.
EIRc, individual energy requirement; RDA, recommended daily allowances; FCS, food consumption survey.
Figures 2a and 2c present the mean values of energy and protein intake according to actual intake of childhood cancer patients, recommended daily allowances (RDA), food consumption survey (FCS) and individual requirements (EIRc and PIRc) at 4 measurement points after diagnosis. Figures 2b and 2d present the patients' energy and protein intake expressed as percentage of EIRc/PIRc, RDA, and FCS.

25-50% of the patients had excess intake (>110% of EIR) (Figure 3). Mean $\%EIR_c$ in tube fed patients was 10.2% (95% CI 0.0; 20.5, $P=0.050$) higher than in orally fed patients.
Compared to RDA, energy intake (kcal/day) of patients was lower at all measurement points (t = -6.03 to -7.13, Z= 5.150, all P values < 0.001) (Figure 2a, table 2) and varied on average from 78% of RDA after diagnosis to 83% after 12 months (Figure 2b). Energy intake (kcal/day) in the patient

Table 2. Energy intake (kcal/day) in age groups according to RDA, FCS and energy intake at the 4 measurement points

Age		Mean RDA		Mean FCS [a]		0 months			3months			6 months			12 months		
		boys	girls	boys	girls	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
0-1 y		500-850	500-850			7	841	372	2	795	71	3	912	241	-	-	-
1-3 y		1200	1125			12	1152	316	9	1153	261	8	1082	304	12	1027	301
	2-3 y			1375	1308												
4-8 y		1720	1550			31	1502	580	27	1460	319	23	1466	269	21	1517	392
	4-6 y			1587	1479												
	7-8 y			1929	2011												
9-13 y		2530	2270	2330	2010	22	1598	729	19	1779	432	17	1757	596	18	1840	423
14-18 y		3350	2500	2622	2008	26	1684	910	17	2035	622	22	1606	541	19	1731	580
0-18 y		-	-			98	1482	714	74	1619	525	73	1511	500	70	1574	519

RDA: recommended daily allowances; FCS: Food Consumption Survey; SD: standard deviation

[a] Data of the Food Consumption Survey (FCS) were available for children aged 2 years and older. The distinct age ranges of the FCS are presented in separate rows.

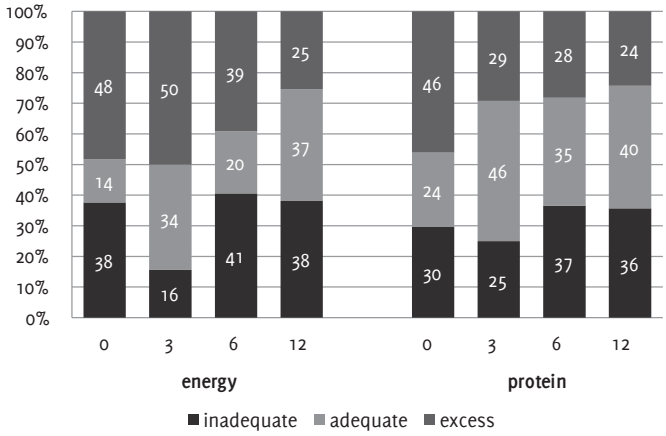


Figure 3. Percentages of patients with adequate, inadequate, or excess intake of energy and protein (based on individual requirements) are presented at 0, 3, 6, and 12 months after diagnosis.

group was lower than in healthy children (FCS) at all measurement points (t= 4.76 to 6.10, all P values < 0.001) (Figure 2a), and ranged from 83% of FCS after diagnosis to 86% after 12 months (Figure 2b).

Protein intake

Mean protein intake was 51 g/day (SD 26) (1.86 g/kg/day) after diagnosis and 54 g/day (SD 21) (1.61 g/kg/day) after 12 months (Table 3). Protein intake did not differ between the measurement points (Multilevel ANOVA F=0.185, P=0.906). Patients' protein intake was higher than their individual requirements (PIR_c) (t= 2.230 to 4.195, P values < 0.05) (Figure 2c). However, at 6 months after diagnosis the difference was not significant (t=1.456 P=.147). Mean $\%PIR_c$ during the study period was 145% and decreased from 154% at the beginning of treatment to 135% after 12 months (estimate slope -2.11 per month, 95%CI -3.35; -.86, P=0.001) (Figure 2d). According to their PIR_c, in the beginning of treatment 30% (29/98) of the patients had an inadequate protein intake, 24% (24/98) had an adequate intake, and 46% (45/98) had an excess intake. After 12 months this was the case in 36% (25/70), 40% (28/70) and 24% (17/70) of the patients respectively (Figure 3). In patients with inadequate protein intake energy intake was generally too low as well. Mean intake of protein accounted for about 14% (SD 3) of total energy intake (En%P). In all patients with adequate energy intake energy percentage of protein was more than 7%. Protein intake

Table 3. Protein intake (g/day) in age groups according to RDA, FCS, and protein intake at the 4 measurement points

Age	Mean RDA		Mean FCS [a]		0 months			3 months			6 months			12 months		
	boys	girls	boys	girls	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
0-1 y	13-22	13-22			7	23	11	2	23	5	3	21	5	-	-	-
1-3 y	14	13			12	35	11	9	38	9	8	35	10	12	29	10
2-3 y			44	44												
4-8 y	22	21			31	54	23	27	47	14	23	51	13	21	51	17
4-6 y			51	51												
7-8 y			61	61												
9-13 y	36	37	75	75	22	55	25	19	58	19	17	57	21	18	63	17
14-18 y	56	49	86	86	26	58	32	17	68	22	22	57	19	19	63	19
0-18 y	-	-			98	51	26	74	53	20	73	51	19	70	54	21
0-18 y (g/kg/day)					98	1.86	1.05	74	1.79	0.80	73	1.67	0.82	70	1.61	0.75

RDA: recommended daily allowances; FCS: Food Consumption Survey; SD: standard deviation

[a] Data of the Food Consumption Survey (FCS) were available for children aged 2 years and older. The distinct age ranges of the FCS are presented in separate rows.

did not differ between orally or tube fed patients (estimate -1.87 (95% CI -18.53; 14.79), P=0.825).
Protein intake was, on average, 181% of RDA (Figure 2d) and was higher than RDA during the whole study period (t= 6.82 to 10.39, all *P* values <0.001) (Figure 2c). Patients' mean protein intake was 88% of intake in healthy children (Figure 2d) and was lower at all measurement points (paired t-tests ranged from -2.62 to -4.17, *P* values < 0.001 to 0.011).

Impact of intake on nutritional status

Mean weight-for-age (WFA), WFH, FM, and %FM increased during the 12 months with 0.25, 0.62, 0.33, and 0.35 SDS respectively, with the steepest increase during the first 3 months; whereas height-for-age (HFA) decreased 0.32 SDS (Table 4) and FFM SDS was low at diagnosis (-0.74 SDS) and remained low. Energy intake (%EIR_c) was negatively associated with WFA, WFH, FM, and %FM. Lean children with low body weight had higher intakes (Table 5). No significant association was found between %EIR_c and HFA or FFM SDS. %PIR_c was not associated with FFM SDS either (estimate -0.001, P=0.369).
Patients with inadequate or excess %EIR_c were not necessarily too thin or too fat. At the 4 measurement points, mean WFH SDS of patients with inadequate %EIR_c was 0.33, 0.33, 0.35 and 0.83 respectively; whereas mean WFH SDS of patients with excess %EIR_c was -0.59, 0.02, 0.07, and -0.04 respectively. Three patients with inadequate %EIR_c were undernourished (WFH< -2SDS) and 8 were overnourished (WFH> 2SDS) at any given measurement point; whereas 9 patients with excess intake were undernourished and 2 overnourished at any given measurement point.

Table 4. Changes in nutritional status in SDS per month[a]

	WFA	WFH	FM	%FM	FFM	HFA
b time	0.02	0.05	0.03	0.03	-0.003	-0.03
95% CI	0.002; 0.03	0.03; 0.06	0.02; 0.05	0.01; 0.05	-0.02; 0.02	-0.04; -0.02
P value	0.026	<0.001	0.037	0.017	0.799	<0.001

SDS, standardized deviation score; WFA, weight-for-age; WFH, weight-for-height; FM, fat mass; %FM, percentage fat mass; FFM, fat free mass; HFA, height-for-age.
[a] Changes were calculated using multilevel analysis and expressed in SDS per month. For example: WFA SDS increased 0.02 SDS (rounded number) per month; so in 12 months WFA increased 0.25 SDS.

Table 5. Associations between energy intake (%EIR_c) and nutritional status[a]

	WFA	WFH	FM	%FM	FFM	HFA
b %EIR_c (95% CI) x 10^{-3}	-2 (-4; -0.3)	-4 (-6; -1)	-4 (-8; -1)	-3 (-6; -0.4)	-1 (-4; 2)	0.8 (-0.3; 2)
P value	0.027	0.004	0.005	0.005	0.417	0.141
b time (95% CI) x 10^{-3}	14 (-2; 29)	38 (20; 56)	19 (-5; 43)	23 (0.7; 46)	-16 (-42; 9)	-28 (-38; -17)
P value	0.089	0.000	0.115	0.044	0.196	0.000

%EIR_c, percentage energy intake of individual requirements; WFA, weight-for-age; WFH, weight-for-height; FM, fat mass; %FM, percentage fat mass; FFM, fat free mass; HFA, height-for-age.
[a] Associations were calculated using multilevel analysis with %EIR_c as covariate and nutritional status as dependent variable. Nutritional status was expressed in standard deviations scores (SDS). The b coefficient of %EIR_c represents the association of energy intake with nutritional status. For example: a 1% increase in EIR_c is associated with a 2 x10^{-3} decrease in WFA SDS. The b coefficient of time represents the slope of the regression analysis as such the change in nutritional status (expressed in SDS) per month.

DISCUSSION

The results of the current study indicate that the energy intake of children treated for cancer broadly matched their calculated individual requirement (EIR_c); whereas according to RDA or intake in healthy controls their intake was inadequate. The gain in weight, WFH, and FM SDS during the 12 months after diagnosis denoted that energy intake was sufficient to meet or even exceeded patients' requirements. Therefore, the norms of RDA and intake in healthy controls are too high for children treated for cancer. The average intake of 105% of EIR_c corresponded with the increase in weight, and it is known that even small increases of 1-2% in energy intake, sustained over a period of time, promote weight gain.[24] To date, EIR_c has been used as a norm only

once before.[5] In that particular study, a mean $\%EIR_c$ of 88% in hematological and 69% in solid malignancies was reported. The lower intake as compared to our study might be caused by cultural differences or by the exclusion of patients receiving tube feeding. Contrary to patients using an oral diet, in tube fed patients energy intake is independent of appetite, and a certain amount of dietary intake is therefore guaranteed.

The findings of our study suggest that, RDA and intake in healthy children are not suitable for this particular group of children. The total energy requirements of childhood cancer patients are diminished[25] because they are less active than healthy children, because their growth in height temporally stagnates, and because their metabolically active body tissue,[26] FFM, is low. This means they require a lower caloric intake than recommended by RDA or than observed in healthy children. However, a definitive answer which of the three norms leads to adequate intake would need a fully fledged RCT design which is on ethical and practical ground very much unlikely to realize.

The current study is the first to assess dietary intake longitudinally during the first year after diagnosis and in the largest sample to date. Taking into account previous research,[4] we expected the lowest intake in the beginning of treatment. However, intake in the early treatment period did not differ from intake at the other measurement points. This might be related to the active treatment policy of our Oncology Department that aims to improve the dietary intake in undernourished children and children at risk for undernutrition by administering energy-enriched food or by feeding children by tube. On average, the first dietary assessment took place 2-3 weeks after diagnosis. By then, most patients had already been visited by a dietitian and had received a tailored dietary advice to improve their intake.

In contrast to the stable energy intake (kcal/day), $\%EIR_c$ decreased during the study period. The relatively high $\%EIR_c$ (111%) at the beginning of treatment can be attributed to the high number of children receiving tube feeding and the relatively low energy requirements. During this particular period the children were very ill and had low levels of physical activity. During the year, however, the children gained weight and became more active, and, as a result, their energy requirements increased. Though their absolute kcal intake remained stable, their $\%EIR_c$ decreased proportionally.

Contrary to our expectations, we found an inverse, albeit weak, relationship between intake and nutritional status. Although energy intake was inadequate in 16-41% of the patients at the different time points, only 3 of those patients were undernourished; whereas 8 were overnourished. Likewise, in patients

with excess intake more patients were undernourished than overnourished. The inverse relationship between intake and nutritional status has been reported previously in survivors as well.[27] One of the underlying explanations could be that lean children with low body weight consumed more food to compensate for previous weight loss during periods of chemotherapy. Moreover, since these children were more often fed by tube feeding, this type of feeding increased their intake. Finally, assessment of dietary intake in children is known to be prone to report-bias too.[28] Whether this report-bias also applies to children with cancer, and thus may have influenced the results of our study, is not known.

Another possible explanation for the absence of a positive relationship between intake and nutritional status might be found in the timing of the assessment. As mentioned before, dietary assessments were conducted between courses of chemotherapy and not during therapy. Presumably, patients experienced alternating periods of poor and good intake; whereas we just registered the good periods. Thus, the registered intake is not representative for the periods during chemotherapy and the actual intake during the whole study period was probably lower.

The relationship between dietary intake and nutritional status has been reviewed by Summerbell et al.[29] The main explanations they found for the absence of a positive relationship were the difficulty in accurately assessing dietary intake and physical activity, and the complexity of the energy balance. Current techniques are insufficiently sophisticated to detect small imbalances that lead to weight gain or weight loss.[29] As such, the calculation of individual energy requirements is only an estimation of the real energy requirements and small errors can have major impact on the calculation's outcome. Moreover, even though Schofield's equation for resting metabolic rate performed excellently at the group level, even in critically ill children; it was less predictive for individuals.[30] Indirect calorimetry is the most reliable tool to assess resting metabolic rate. Unfortunately, this method is labor-intensive and burdensome to this particular patient group[31] and as such not suitable for daily practice. Therefore, for this moment, we consider the calculation of individual requirements using Schofield's equation as the best starting point to determine adequate energy intake. Further research is needed for the development of a prediction formula specifically aimed at childhood cancer. Given the heterogeneity of the patient group and alternating course of the disease, there can be little doubt that this will be a great challenge.

Apart from the results concerning energy intake, we found that protein intake

in childhood cancer patients was lower than in healthy children. However, protein intake was almost twice the recommended allowances and one and a half times the individual requirements. Previous studies have reported similar results.[32,33] The high protein intake may be interpreted as a positive finding, given the risk for loss of FFM during cancer treatment. However, the protein intake had no beneficial effect on FFM; FFM was low at the beginning of treatment and remained low. It is not unlikely that the protein requirements needed to improve FFM are higher than the current recommendations. Thus far, it is unknown whether excess protein intake has negative consequences for this patient group. High protein intake has been linked to a decline in renal function, but only in individuals with preexisting renal problems.[10] Despite the high protein intake on average, protein intake was inadequate in about one third of the patients at the different measurement points. Since energy intake in these patients was generally inadequate as well, these patients were particularly at risk for muscle wasting.

Finally, we believe the results of the current study are also applicable to other industrialized countries, since the Dutch RDA are largely in line with the RDA of other countries, such as the United States and Great-Britain.[20]

In conclusion, the outcomes of the adequacy of energy and protein intake differed considerably according to the three norms. Given the increase in weight during the course of treatment, excess intake was more prevalent than inadequate intake. The percentage intake of individual energy requirements ($\%EIR_c$) corresponded to weight gain; whereas the norms of RDA and intake in healthy controls were too high. Our results indicate that, childhood cancer patients require less energy than RDA and less energy than healthy children. Therefore, to determine the adequacy of dietary intake in both clinical practice and futures studies the use of individual requirements is recommended as a starting point instead of RDA or intake as observed in healthy controls.

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SUPPLEMENT

Calculation individual energy requirements:
EIR_c = (RMR x PAL x GF)/EAC[1]

EIR_c = individual energy requirements
RMR = resting metabolic rate
PAL = physical activity level
GF = growth factor
EAC = energy absorption coefficient

Table 1. Resting metabolic rate (Schofield-equation for kcal/day)[1]

Age	Boys	Girls
0-3 year	0.167 (weight) + 1516.7 (height) - 617.3	16.2 (weight) + 1022.7 (height) - 413.3
3-10 year	19.6 (weight) + 130.2 (height) + 414.7	17.0 (weight) + 161.7 (height) + 371.0
10-18 year	16.2 (weight) + 137.1 (height) + 515.3	8.4 (weight) + 465.4 (height) + 200.0

weight in kg; height in meters

Table 2. Physical activity level based on Lansky Play Performance Scale.[2]

	Lansky PPS	PAL[1]	
		Child	Infant
100%	Fully active.[a]	1.5	1.3
90%	Minor restriction in physically strenuous play.	1.5	1.3
80%	Restricted in strenuous play, tires more easily, otherwise active.	1.3	1.3
70%	Both greater restrictions of, and less time spent in, active play.	1.1	1.1
60%	Ambulatory up to 50% of the time, limited active play with assistance/supervision.	1.1	1.1
50%	Considerable assistance required for any active play; fully able to engage in quiet play.	1.0	1.0
40%	Able to initiate quiet activities.	1.0	1.0
30%	Needs considerable assistance for quiet activity.	1.0	1.0
20%	Limited to very passive activity initiated by others (i.e.TV).	1.0	1.0
10%	Completely disabled, not even passive play.	1.0	1.0

[a] For children performing (strenuous) sports activities, PAL can increase to 1.7-2.1. However, since none of the childhood cancer patients participated in sport activities during the study period, the maximum PAL was set at 1.5.

Table 3. Growth factor.[1]

Age phase of the child	Growth factor
Premature	1.30
Infant < 4 months	1.30
Infant > 4 months	1.10
Child 1-2 year	1.02-1.04
Child > 2 year	1.02
Pubertal growth spurt	1.04
During peak	1.20

Table 4. Energy absorption coefficient of healthy children.[1]

Age	Absorption coefficient
Premature neonate	0.60-0.75
Normal neonate	0.80-0.85
0-3 years	0.85-0.95
> 3 years	0.95-0.98

Table 5. Recommended protein intake (g/kg/day) and energy percentage protein.[3,4]

Age	Protein (g/kg/day) [a]		En% [a]	
	Boys	Girls	Boys	Girls
0-2 mo	1.8	1.8	8	8
3-5 mo	1.4	1.4	7	6
6-11 mo	1.2	1.2	6	6
1-3 year	1.2	1.2	5	5
4-8 year	1.2	1.2	5	5
9-13 year	1.2	1.2	6	6
14-18 year	1.2	1.2	7	8

[a] The RDA for protein is based on the recommended dietary allowances (=mean + 2SD)

Table 6. Recommended Daily Allowances (RDA) for energy and protein.[4]

Age	Energy (kcal/d)[a]		Protein (g/d)[b]	
	Boys	Girls	Boys	Girls
0 - 1/2	500	500	13	13
1/2 - 1	850	850	22	22
1-3	1200	1125	14	13
4-8	1720	1550	22	21
9-13	2530	2270	36	37
14-18	3350	2500	56	49

[a] The RDA for energy is based on the average requirement (=mean)
[b] The RDA for protein in based on the recommended dietary allowances (=mean + 2SD)

Table 7. Energy and protein intake in healthy Dutch children according to the Dutch National Food Consumption Survey[5,6] (median values are presented).

Age	Energy (kcal/d)		Protein (g/d)	
	Boys	Girls	Boys	Girls
2-3	1375	1308	44	43
4-6	1587	1479	51	46
7-8	1929	2011	61	60
9-13	2330	2010	75	64
14-18	2622	2008	86	67

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CONSEQUENCES OF MALNUTRITION

CHAPTER 6

CLINICAL IMPLICATIONS OF MALNUTRITION IN CHILDHOOD CANCER PATIENTS: INFECTIONS AND MORTALITY

Erik A.H. Loeffen
Aeltsje Brinksma
Karin G.E. Miedema
Truuske G.H. de Bock
Wim J.E. Tissing

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ABSTRACT

Purpose: In childhood cancer patients, malnutrition has been proposed to increase infection rates and reduce survival. We investigated whether malnutrition at diagnosis and during treatment and weight loss during treatment are prognostic factors for infection rates and survival, within a heterogeneous childhood cancer population.

Methods: From two previous studies, all children ≤ 18 years of age diagnosed with cancer between October 2004 and October 2011 were included in this study. Data regarding BMI, infections and survival were retrieved. Patients with a BMI z-score lower than -2.0 were classified as malnourished. Weight loss more than 5% was considered relevant.

Results: 269 childhood cancer patients were included in this study. At diagnosis, 5.2% of all patients were malnourished. These patients showed worse survival than those who were well nourished (HR=3.63, 95% CI=1.52-8.70, p=0.004). Malnourishment at three months after diagnosis (3.3% of all patients) also showed worse survival (HR=6.34, 95% CI=2.42-16.65, p<0.001). Weight loss of more than 5% in the first three months after diagnosis was related to increased occurrence of febrile neutropenic episodes with bacteraemia in the first year after diagnosis (OR=3.05, 95% CI=1.27-7.30, p=0.012).

Conclusion: We found that malnourishment in the initial phase of therapy is associated with worse survival in childhood cancer patients. In addition, we found for the first time that weight loss during treatment is associated with increased presence of febrile neutropenic episodes with bacteremia. This underlines the importance of optimal feeding designs in childhood cancer patients.

INTRODUCTION

Childhood cancer is an illness related to severe morbidity and mortality. The malignancy itself remains the main cause of death in childhood cancer patients.[1,21,2] However, infectious complications, especially during chemotherapy induced neutropenia, also account for a large part of morbidity and mortality (two in every three treatment related deaths) and could be potentially preventable.[3,4] Moreover, infections lead to delay of treatment or dose reduction of chemotherapy, which causes suboptimal treatment and might thus lower survival chances. It has been hypothesized that malnutrition lowers defensibility of childhood cancer patients against infections, for instance by causing hormonal changes and compromised cytokine response.[5,6] Secondly, it has been proposed that nutritional status might be an influential factor on mortality.[7,8] When undergoing treatment, malnutrition could lower effectiveness of anti-cancer treatment, by ways of suboptimal tolerated dose intensity and reduced absorption of chemotherapeutical drugs.[9] In previous studies, higher relative risks of death for malnourished as well as overnourished children diagnosed with ALL have been found.[7,8]

There are still profound gaps in knowledge regarding malnutrition in childhood cancer patients, e.g. causes, frequencies and consequences. Studies in this area provide little solid information, due to small sample sizes and the use of different methods and cut-off values to assess nutritional status.[10] Moreover, studies on the effect of malnutrition on both infections and mortality has been done in homogenous patient groups including patients with one diagnosis. Thereby a specific effect of malnutrition in only the specific patient group cannot be excluded.

The goal of this study is to explore the role of malnutrition in respect to survival and infectious risk, i.e. the presence of febrile neutropenia in all children with cancer. This might lead to new insights in the treatment of childhood cancer.

PATIENTS AND METHODS

This study was performed at the Department of Pediatric Oncology/ Hematology of the University Medical Center Groningen (UMCG). Primary care for childhood cancer patients is situated in the UMCG, with multiple

shared care centers in the area providing outpatient chemotherapy, possibility for admission in case of febrile neutropenia and follow-up.

Patients

From two previous studies on nutritional status (Pecannut study[11]) and febrile neutropenia (IL-8 study, data not yet published) in childhood cancer, all children ≤ 18 years diagnosed with a malignancy between October 2004 and October 2011 were included in the present study. Patients diagnosed in the UMCG but primarily treated in another pediatric oncological hospital were excluded from this study.

For both the IL-8 and the Pecannut study, written informed consent was given by all patients and/or parents, and approval was given by the medical ethical review committee of the UMCG.

Data collection

Most data regarding nutritional status, survival and infections used in this study were retrieved from the IL-8 and the Pecannut study. Data regarding admissions for febrile neutropenia and body mass index (BMI) at four moments (at diagnosis, and three months, six months and twelve months after diagnosis) were collected from the study records. Medical records were then searched for missing data and additional data for this study. Shared care centers were contacted and visited for completion of the database, i.e. local admissions for febrile neutropenia.

Definitions

For every patient, all admissions for febrile neutropenic (FN) episodes in the first year after diagnosis were analysed. In accordance with previous studies on FN episodes, febrile neutropenia was defined as the combination of a single body temperature >38.5°C (or two or more recordings >38.0°C during a 6 hour period) and an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L (or when lacking, a leukocyte count $<1.0 \times 10^9$/L).[12,13] FN episodes were divided into two groups; fever of unknown origin or bacteremia. Bacteremia was defined as the isolation of a bacterial pathogen from a blood sample. Complications were defined as admission to an intensive care unit or death.

Regarding nutritional status, BMI z-scores were calculated using Growth Analyser VE 1.3.2 (© Growth Analyser BV, The Netherlands), with "The Netherlands 2010, BMI for age" serving as reference. The BMI z-score reflects how patients related to contemporary, Dutch children of the same age and

sex. Regarding BMI z-score at diagnosis, cutoff values for malnourishment and overnourishment were chosen as −2.0 and 2.0, respectively. Cutoff values -1.5, -1.0, -0.5, 0.5, 1.0 and 1.5 were also analysed to identify clinically relevant cutoff values. Information regarding the clinical relevance of weight loss in the field of childhood cancer is lacking.[10] In adult medicine, however, it is a clinically widely used variable.[14] Therefore, we chose to also analyse weight loss. Weight loss >5%, or a decrease ≥1.0 in BMI z-score, in the first three months after diagnosis was considered relevant.
Major endpoints were overall survival and number of FN episodes, with or without bacteremia.

Statistical analysis

Due to the variety of diagnoses in our population, numbers of patients in diagnosis specific subgroups were relatively small. Correcting for all these subgroups separately was not realistic and statistically not feasible. Therefore, patients were classified based on expected survival based on diagnosis (for survival analysis) and intensity of treatment (for infection analysis). With regard to expected survival based on diagnosis, we developed a variable to correct for the variance in prognosis. Literature was combined with the expert-opinion of three pediatric oncologists of our hospital. All diagnoses, and if applicable different stages, were classified in five-year survival rates < 40 %, 40 − 60 %, or > 60 % (see supplementary data). Concerning the intensity of treatment, the four level Intensity of Treatment Rating Scale 3 (ITR-3) was used.[15] Three minor modifications to this scale were made (see supplementary data).
Survival was defined as time from diagnosis till death. Patients who were still alive at the end of follow-up, or lost to follow-up were censored. The Kaplan-Meier method was used to depict survival curves.[16] Differences between groups on survival were estimated in univariate and multivariate Cox regression analyses, yielding hazard ratios (HRs) and 95% confidence intervals (CIs).[17,18]
To investigate whether nutritional status at diagnosis and weight loss during treatment were prognostic factors for infection rates during the first year, patients who did not receive chemotherapy (n=20), and were therefore not susceptible to chemotherapy induced neutropenia, were excluded from analysis. Differences between groups regarding presence of infections were estimated in univariate and multivariate binary logistic regression, yielding odd ratios (ORs) and 95% CIs.

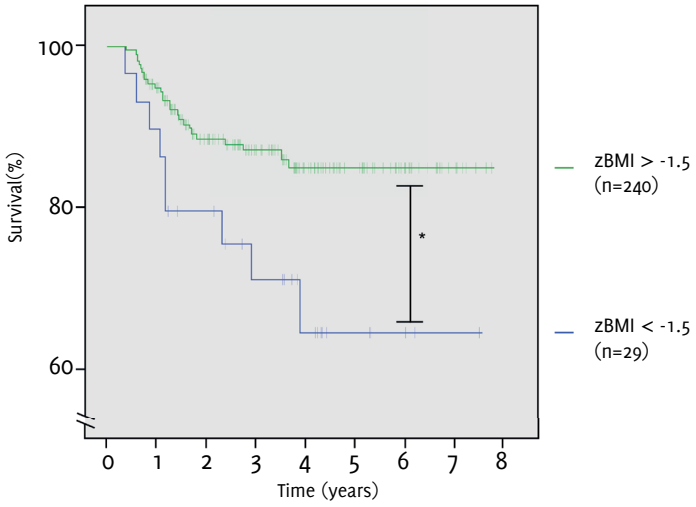

Figure 1. Kaplan-Meier survival curve of patients by BMI z-score at diagnosis. * Logrank test: Chi^2=6.116, p=0.013.

The significance level of all tests was determined at $p<0.05$. Statistical analyses were performed using IBM SPSS version 20.0.0.1 (International Business Machines Corporation, NY, USA).

RESULTS

Patient characteristics

A total of 269 childhood cancer patients receiving treatment for a malignancy were included in this study. Their characteristics are shown in table 1. Median follow-up from diagnosis was 3 years and 8 months (range: 8 months – 7 years and 8 months). At the moment of analysis, 43 patients had died, 199 had finished treatment and 27 were still receiving treatment. Twenty-six patients underwent hematopoietic stem cell transplantation (HSCT), of which 19 were autologous and 7 were allogeneic. Main cause of death was

Table 1. Patient and disease characteristics (n = 269).

Characteristic		
Age at diagnosis in years (median, range)	7.4	(0-17.7)
Follow up in days (median, range)	1326	(243-2804)
	n	**(%)**
Male patients	137	(51)
Hematological malignancy	139	(52)
Solid tumor	86	(32)
Brain tumor	44	(16)
Number of admissions because of febrile neutropenic episodes in the first year after diagnosis[a]	332	(100)
Number of admissions for FN per patient (median, range)	1	(0-7)
Fever of unknown origin	250	(75)
Bacteremia[b]	82	(25)
Febrile neutropenic episodes with complication[c]	42	(13)

[a] Neutropenia is defined as an absolute neutrophil count (ANC) < 0.5 x 109/L or, in the absence of an ANC, a leukocyte count < 1.0 x 109/L.
[b] Bacteremia is defined as the isolation of a bacterial pathogen from a blood sample.
[c] Complication is defined as death or admission to an intensive care unit during febrile episode.

malignancy itself (n=35), followed by infection (n=4) and other causes (n=4; 1 cerebral infarction, 1 graft versus host disease after hematopoietic stem cell transplantation (HSCT), 1 virus reactivation after HSCT, 1 unknown complication of treatment).

Nutritional status

Nutritional status of male and female patients at diagnosis did not differ significantly (p=0.721). At diagnosis, 14 patients (5.2%) were malnourished (BMI z-score < -2), 229 patients (56.9%) were well-nourished, and 19 patients (7.1%) were overnourished (BMI z-score > 2).
Gender and diagnosis had no significant influence on weight loss and BMI z-score decrease (Table 2). Weight loss increased with patients growing older. Significantly more patients in the oldest group (age > 10 years) lost more than 5% weight in the first three months after diagnosis than younger patients (p=0.017). BMI z-score decrease showed no difference between all age groups.

Table 2. Nutritional status changes.

	Weight loss† (n=259)		BMI z-score decrease† (n=251‡)	
	> 5% (n=32)	≤ 5% (n=227)	> 1.0 (n=15)	≤1.0 (n=236)
	n (%)	n (%)	n (%)	n (%)
Male	15 (11)	120 (89)	6 (4)	126 (96)
Female	17 (14)	107 (86)	9 (8)	110 (92)
Age < 4 yrs	5 (7)	66 (93)	6 (9)	63 (91)
Age 4 – 10 yrs	9 (10)	84 (90)	5 (5)	87 (95)
Age > 10 yrs	18 (19)*	77 (81)	4 (4)	86 (96)
Hematological	16 (12)	121 (88)	4 (3)	126 (97)
Solid	12 (14)	71 (86)	7 (9)	75 (91)
Brain	4 (10)	35 (90)	4 (10)	35 (90)

† In first three months after diagnosis; ‡ From 8 patients no data regarding height, and thus BMI z-score, was available; * OR=3.086, 95% CI=1.086-8.765, p=0.034

Associations between nutritional status and survival

Regarding nutritional status, survival was significantly worse (p=0.01) for patients who were malnourished at diagnosis (n=14) than for those who were well- and overnourished at diagnosis (n=248) (Table 3). In a multivariate analysis that included BMI z-score at diagnosis and expected survival based on diagnosis, malnourishment remained its significance (HR=3.63, 95% CI=1.52-8.70, p=0.004). Patients with a BMI z-score below -1.5 (n=29) also showed significantly worse survival (HR=2.22, 95% CI=1.05–4.68, p=0.037) than those above -1.5 (n=233). For patients below -1.0 (n=52) versus those above -1.0 (n=210), no difference in survival was observed (HR=1.37, 95% CI=0.67-2.81, p=0.392).

Regarding nutritional status at 3 months, malnourishment also decreased survival significantly. In multivariate analysis including BMI z-score at 3 months and expected survival based on diagnosis, survival was significantly worse (HR=6.34, 95% CI=2.42-16.65, p<0.001) for patients with a BMI z-score below -2.0 (n=9) versus those above -2.0 (n=260).

Survival was also worse for patients with a BMI z-score at 3 months below -1.5 (n=20) versus above -1.5 (n=249) (HR=3.22, 95% CI=1.27-8.11, p=0.013), as well as below -1.0 (n=29) versus above -1.0 (n=240) (HR=2.39, 95% CI=1.02-5.59, p=0.044). Survival did not differ significantly (HR=1.11, 95% CI=0.56-2.21, p=0.772) between patients with a BMI z-score at 3 months below -0.5 (n=59) and those above -0.5 (n=210).

Overnourishment at diagnosis, nutritional status at 6 and 12 months, and changes in nutritional status did not influence survival (Table 3).

Table 3. Nutritional status and changes hereof, and relation to survival (n=269).

	Survival status at moment of analysis†						
	Deceased (n=43)		Alive (n=226)				
	n	(%)	*n*	(%)	HR‡	95% CI‡	*p*‡
Gender							
Female	23	(17)	109	(83)	1		
Male	20	(15)	117	(85)	0.827	0.454-1.507	0.536
Age							*0.619*
< 4 yrs	14	(19)	60	(81)	1		
4 - 10 yrs	14	(15)	80	(85)	0.717	0.342-1.504	0.378
> 10 yrs	15	(15)	86	(85)	0.738	0.356-1.529	0.413
Diagnosis							*0.002*
Hematological	11	(8)	128	(92)	1		
Solid	20	(23)	66	(77)	3.355	1.606-7.010	*0.001*
Brain	12	(27)	32	(73)	3.677	1.621-8.338	*0.002*
Expected five-year survival based on diagnosis							*0.000*
> 60 %	22	(10)	193	(90)	1		
40 – 60 %	5	(19)	22	(81)	1.897	0.718-5.010	0.196
< 40 %	16	(59)	11	(41)	8.767	4.563-16.842	*0.000*
BMI z-score at diagnosis							*0.010*
-2.0 – 2.0	26	(14)	165	(86)	1		
> 2.0	3	(16)	16	(84)	1.150	0.351-3.768	0.818
< -2.0	6	(43)	8	(57)	3.904	1.624-9.388	*0.002*
BMI z-score at 3 months							
≥ -2.0	38	(15)	222	(85)	1		
< -2.0	5	(56)	4	(44)	5.348	2.101-13.611	*0.000*
BMI z-score at 6 months							
≥ -2.0	42	(16)	221	(84)	1		
< -2.0	1	(17)	5	(84)	0.937	0.129-6.815	0.949
BMI z-score at 12 months							
≥ -2.0	41	(16)	214	(84)	1		
< -2.0	2	(14)	12	(86)	0.912	0.220-3.772	0.899
*Weight loss**							
≤ 5 %	30	(17)	142	(83)	1		
> 5 %	8	(9)	79	(91)	1.134	0.442-2.906	0.794
*BMI z-score decrease**							
≤ 1.0	35	(15)	201	(85)	1		
> 1.0	4	(26)	11	(74)	2.054	0.730-5.781	0.173

† Follow up in days (median, range): 1186 (17-2804); ‡ Univariate cox regression test comparing survival among groups; * In first three months after diagnosis.

Table 4. Nutritional status and changes hereof, and relation to FN episodes with bacteremia (n=249).

	Number of episodes of FN with bacteremia in year 1 after diagnosis						
	> 0 (n=60)		0 (n=189)				
	n	(%)	n	(%)	OR‡	95% CI‡	p‡
Gender							
Female	33	(27)	91	(73)	1		
Male	27	(22)	98	(78)	0.760	0.424-1.361	0.356
Age							*0.000*
< 4 yrs	29	(42)	40	(58)	1		
4 - 10 yrs	16	(17)	76	(83)	0.283	0.136-0.590	*0.001*
> 10 yrs	15	(17)	73	(83)	0.290	0.141-0.597	*0.001*
Diagnosis							
Hematological	34	(24)	105	(76)	1		
Solid	20	(24)	64	(76)	0.965	0.512-1.819	0.912
Brain	6	(23)	20	(77)	0.926	0.344-2.496	0.880
Intensity of treatment rating							*0.000*
Level 1+2	20	(15)	114	(85)	1		
Level 3	28	(30)	66	(70)	2.418	1.264-4.627	*0.008*
Level 4	12	(63)	9	(37)	7.600	2.835-20.377	*0.000*
*BMI z-score**							0.539
-2.0 – 2.0	16	(21)	59	(79)	1		
> 2.0	3	(17)	15	(83)	0.589	0.164-2.113	0.417
< -2.0	2	(15)	11	(85)	0.535	0.115-2.492	0.426
*Weight loss***							
< 5 %	44	(21)	167	(79)	1		
> 5 %	14	(44)	18	(56)	2.952	1.362-6.397	*0.006*
*BMI z-score decrease***							
< 1.0	49	(22)	173	(78)	1		
> 1.0	7	(54)	6	(46)	4.119	1.323-12.823	*0.015*

‡ Univariate binary logistic regression comparing presence of FN episodes among groups.
* At diagnosis; ** In first three months after diagnosis.

Associations between nutritional status and febrile neutropenia

A total of 332 admissions for febrile neutropenia occurred in the first year after diagnosis. Malnourishment at diagnosis was not associated with admissions for febrile neutropenia in the first year after diagnosis ($p=0.495$), neither was overnourishment at diagnosis ($p=0.324$). A decline >1.0 in BMI z-score or weight loss >5% in the first three months after diagnosis did not increase FN episode rates ($p=0.432$ and $p=0.102$, respectively).

Of all 332 FN episodes, 82 episodes (24.6%) showed bacteremia. Regarding occurrence of these episodes, there were no differences between patients who were well nourished at diagnosis, and patients who were malnourished or overnourished at diagnosis. However, patients who declined >1.0 in BMI z-score in the first three months after diagnosis ($n=13$) had significantly more FN episodes with bacteremia in the first year after diagnosis ($p=0.010$) (Table 4). In multivariate analysis that included decline in BMI z-score, age and intensity of treatment, decline in BMI z-score >1.0 was nearly significant (OR=3.366, 95% CI=0.99-11.4, $p=0.052$).

Weight loss >5% in the first three months after diagnosis showed a strong association with the occurrence of FN episodes with bacteremia in the first year after diagnosis ($p=0.004$). In multivariate analysis, including intensity of treatment and age, this association persisted (OR=3.05, 95% CI=1.27-7.30, $p=0.012$). Weight loss between 3 and 6 months, and between 6 and 12 months did not influence occurrence of FN episodes.

Nutritional status and changes hereof showed no significant relation with complications during FN episodes.

DISCUSSION

In this study we demonstrated in a large, heterogeneous childhood cancer population, that those patients who were malnourished at diagnosis or at three months after diagnosis had significantly worse survival. Furthermore, we showed increased rates of febrile neutropenic episodes with bacteremia in the first year after diagnosis in childhood cancer patients who lost more than 5% of their body weight in the first three months after diagnosis.

The association of malnourishment with lower survival rates in childhood cancer patients has been found in previous studies in homogenous patient populations (i.e. only one diagnosis).[4,19,20] The present study confirms this association, independent of expected survival based on diagnosis, in a

heterogeneous childhood cancer population. This implies that there is an effect over all pediatric cancer diagnoses, and not only in patients with AML or rhabdomyosarcoma as studied before. Both malnourishment at diagnosis and malnourishment at three months after diagnosis were related to reduced survival rates. Unlike malnourishment at diagnosis, malnourishment at three months after diagnosis is possibly preventable by close monitoring of the nutritional status and swift intervention if necessary. This could contribute to increased survival rates. In contrast to previous studies, in the present study overnourishment did not play a role in survival.[8,20]

Secondly, we showed, for the first time, that weight loss in the first three months after diagnosis is associated with increased rates of FN episodes with bacteremia in the first year after diagnosis. Rapid loss of weight appears to make childhood cancer patients more vulnerable for bacterial infections. This knowledge might help identify patients that are at risk. In addition, this finding underlines the importance of the parameter weight in this patient population.

Limitations

Although this study gives new insight in the role of nutritional status in childhood cancer, there are certain points that should be taken into account when interpreting these findings. The retrospective character of this study can be considered a limitation, although it should be noted that all patients were already prospectively included in another study and thus thoroughly and regularly monitored.

This study investigated the implications of nutritional status in a heterogeneous childhood cancer population. Thus far, most studies in this area investigated patient groups with one specific type of cancer. This makes their results, in contrast to our findings, not applicable to childhood cancer patients in general. A possible disadvantage of the heterogeneity is the fact that different malignancies have different presentations, courses and treatments. This was taken into account by the use of intensity of treatment rating and expected survival based on diagnosis classification in the respective analyses.

To overcome these disadvantages, future studies should be prospective case-control studies, including larger patient numbers.

Assessment of nutritional status

Nutritional status can be examined in multiple ways. In this study, body mass index (BMI) z-scores were used. Multiple studies promote the use of BMI as

indicator of nutritional status, because its measurements are simple, quick, non-expensive, non-invasive and have low inter-observer variability.[10,19,21,22] To date there is no agreement on the criteria regarding nutritional status assessment, such as the percentage weight loss that is clinically relevant.[23] This makes it difficult to determine cut-off values, and even more difficult to compare different studies. Nevertheless, a cut-off value is determined by its clinical relevance. In this study, clinically relevant cut off values were -1.5 for BMI z-score at diagnosis in relationship to decreased survival rates, -1.0 for BMI z-score at 3 months in relationship to decreased survival rates, and weight loss >5% in the first three months after diagnosis in relationship to increased rates of FN episodes with bacteremia in the first year after diagnosis. In conclusion, childhood cancer patients presenting with malnourishment in the initial phase of therapy showed a significant worse survival, independent of expected survival based on diagnosis. Regarding infections we were the first to show that rapid weight loss after diagnosis is associated with the occurrence of significantly more febrile neutropenic episodes with bacteremia, hereby establishing the clinical relevance of this parameter and cut-off value. Our findings regarding the role of nutritional status at three months and rapid weight loss suggest that prompt correction of nutritional status in children receiving anti-cancer treatment might improve survival as well as infectious outcome.

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“Ik kan niet goed lopen of rennen, maar zoals ik me op dit moment voel vind ik wel een 10: ik kan uit bed, zelf tandenpoetsen, ik kan naar beneden, ik ben superblij zoals het nu gaat. Ik heb er geen problemen mee. Maar zoals ik me nu voel zou ik niet willen leven, want ik ben snel moe, maar het is het best denkbare voor dit moment.”

jongen, 14 jaar

CHAPTER

7

EXPLORING THE RESPONSE SHIFT PHENOMENON IN CHILDHOOD CANCER PATIENTS AND ITS EFFECT ON HEALTH-RELATED QUALITY OF LIFE

Aeltsje Brinksma
Wim J.E. Tissing
Esther Sulkers
Willem A. Kamps
Petrie F. Roodbol
Robbert Sanderman

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ABSTRACT

Purpose/Objectives : To explore the response shift phenomenon in childhood cancer patients and to determine its effects on the ratings of health-related quality of life (HRQOL).

Design: Retrospective pretest-posttest design.

Setting: Pediatric oncology department in the northern part of the Netherlands.

Sample: 37 children newly diagnosed with cancer and 80 parents.

Methods : The then-test method was used to determine response shift. HRQOL was assessed within two weeks after diagnosis (pretest) and three months later (post-test) using both child- and parent report of PedsQL and Cantril's ladder. The post-test and then-test were administered concurrently.

Main research variables: Overall and multidimensional HRQOL.

Findings: Scores on Cantril's then-test were lower than the pretest in both child and parent reports, indicating response shift in the assessment of overall HRQOL. Children experienced a greater response shift than parents. No differences were found between the PedsQL then- and pretests.

Conclusions: Both child- and parent-report ratings of overall HRQOL were affected by response shift, resulting in an underestimation of the improvement in overall HRQOL between diagnosis and three months post-diagnosis. No response shift was demonstrated in the more specific domains of HRQOL (PedsQL).

Implications for nursing: Knowledge of the response shift phenomenon helps nurses to better interpret the outcomes of HRQOL. The use of the PedsQL instruments is recommended in future studies that aim to demonstrate changes in HRQOL.

INTRODUCTION

The Health Related Quality of Life (HRQOL) is important for understanding the impact of cancer on a child's life. HRQOL is defined as "a multi-dimensional construct that includes physical, social and emotional functioning of the child, measured from the perspective of both the child and his/her family, and sensitive to the changes that occur throughout development."[1] To determine deterioration or improvement in HRQOL during treatment, the reference point for good or poor HRQOL should be the same at all measurement points. However, because the measurement of HRQOL relies on self-report, the rating depends on an individual's perception of HRQOL at the time of measurement. This perception might change over time. Being confronted with cancer, for instance, can change an individual's perception about good and poor HRQOL due to adaptation to the imperfect health status.[2] Consequently, individuals may report good levels of HRQOL despite deterioration in their health status, and in contrast to what nurses expect. Several studies have demonstrated that cancer patients reported levels of HRQOL similar to healthy persons.[3] In childhood cancer patients, psycho-social HRQOL was often found to be even higher than in healthy children.[4,5] This phenomenon of adaptation to a change in health status is called response shift. The response shift phenomenon has been found in adult cancer patients.[6-12] However, research on the influence of response shift on HRQOL ratings in childhood cancer patients is lacking. Response shift is defined as "a change in the meaning of one's self-evaluation of a target construct as a result of changes in internal standards (scale recalibration), values (reprioritization), or a redefinition of the target construct (reconceptualization)."[13,14]

Although response shift is a natural way to cope with and adapt to changes in health status,[15] it generates a bias in consecutive measurements of HRQOL. As a result, treatment effects on the child's HRQOL can be reduced or inflated. Moreover, when studying a nursing intervention aiming to improve HRQOL the outcome might be underestimated when the endpoint parameter is subject to response shift.

Because the HRQOL of children is preferably measured using both child and parent report,[16] both ratings might be influenced by response shift. Proxy-measurement is considered to be less sensitive to response shift, because proxy-raters do not experience the imperfect health status themselves.[2] However, whether this is true for parents of critically ill children is unknown because childhood cancer has a major impact on the parents as well.

In this study we will assess the impact of response shift on the assessment of HRQOL in childhood cancer at the level of overall impression of HRQOL, because this level is known to be sensitive to response shift in adults,[17] and second, at the more specific level of the domains of HRQOL. This level, consisting of the physical, social and emotional domains of HRQOL, is most commonly used in HRQOL assessment. This study aims: (1) to determine the change in health status and HRQOL during the first three months after diagnosis; (2) to examine whether the HRQOL ratings are affected by response shift; and (3) to determine similarities and differences with regard to the presence, direction, and magnitude of response shift between child- and parent-report ratings.

METHODS

Participants

Data were collected as part of a prospective cohort study of newly diagnosed cancer patients at the University Medical Center Groningen (UMCG) in the Netherlands. Ethical approval was gained from the Medical Ethics Committee of the UMCG. Between September 2007 and December 2009, all patients aged 2-18 years consecutively admitted to the Pediatric Oncology Department were asked to participate. Exclusion criteria were: having insufficient command of the Dutch language or being in a palliative phase of treatment. The response shift study was restricted to children aged 8 years and older and their parents for child- and parent-report. Parents of children between 2-7 years old were included for parent report only. A total of 121 parents and 61 children were eligible and were invited to participate. Fifty-one children and 100 parents gave informed consent. Response rate was 83.6% for child report and 83% for parent report. Reasons for declining child report were: too burdensome (n=6) and lack of motivation (n=4), and for parent report: too burdensome (n=17) and lack of motivation (n=4). After inclusion, 7 children dropped out (too burdensome (n=2), lack of motivation (n=3), or being too ill (n=2)), and the data of another 7 children were incomplete. Fifteen parents dropped out (too burdensome (n=5), lack of motivation (n=8), child is too ill (n=2)), and the data of 5 parents were incomplete. Finally, 37 child-parent pairs completed all measurements as well as 43 parents of younger children. Only complete data sets including all measurements were used for analysis.

Procedure

The most widely used method to examine response shift is the then-test method, also known as the retrospective pretest-posttest design method.[14,18,19] In this method, individuals are asked to evaluate their HRQOL at the pretest and the post-test. Immediately following the post-test, the then-test is administered; whereby individuals are instructed to reassess their pretest HRQOL. They are not asked to remember their pretest rating, but to retrospectively give a renewed judgment about their HRQOL at the pretest. Because the then-test is completed at the same time as the post-test, respondents would likely use the same internal standards. A difference between the then-test and the pretest provides evidence of recalibration of HRQOL between pre- and post-test measurement. In this study, HRQOL was assessed within two weeks after diagnosis (pretest) and three months later (post-test). For administering the then-test, parents received written instructions to take the first week after diagnosis in mind when filling out the then-test. The researcher asked children to recall the period shortly after diagnosis and to name special events from that period. When children indicated they could vividly remember this period, the then-test was administered by interview.

Measures

Health status was assessed by the Lansky Play Performance scale (PPS),[20] a 10-point parent-rated Likert-scale recording the daily play activity of the child ranging from fully active (100), to completely disabled, not even passive play (10). The PPS has adequate reliability (mother versus father ratings, r = 0.71) and content validity (parent versus nurses ratings, r = 0.75).[20] The Memorial Symptom Assessment Scale (MSAS)[21,22] was used for reporting the number of symptoms children experienced. The MSAS is a child- and parent-rated instrument consisting of 30 of the most common symptoms experienced during cancer treatment and has demonstrated reliability (r = 0.83-0.87) and validity (high correlations with other symptom instruments and higher symptom number among patients who had recent chemotherapy) in childhood cancer populations.[21] Crohnbach alpha in the present sample was r = 0.80 and 0.75 for child-reported pre- and post-test and r = 0.85 and 0.83 for parent-reported pre- and post-test, respectively.

HRQOL was assessed by means of Cantril's ladder and PedsQL instruments. Cantril's ladder[23] is a single item Visual Analog Scale rating the overall impression of Quality of Life on a scale of 0-10, where 10 represents the best possible quality of life and 0 the worst possible quality of life. Cantril's

ladder was used as pre-, post-, and then-test. Although Cantril's ladder has frequently been used in many studies, no data for reliability and validity have been reported.

The PedsQL 4.0 Generic Core Scale[24,25] is a 23-item multidimensional scale designed to measure HRQOL in children and adolescents aged 2-18 years old. The PedsQL Cancer Module[26] is a 27-item scale developed to measure pediatric cancer specific HRQOL. The PedsQL instruments are comprised of parallel child self-report formats (ages 5 and older) and parent proxy-report formats (ages 2 and older) and have high levels of internal consistency ranging from r = 0.72-0.88 for child report and r = 0.86-0.90 for parent report. Validity was demonstrated using the known-groups method; the PedsQL instruments distinguished between healthy children and children with cancer.[24-27] For the then-test a selection of 14 items from both PedsQL instruments (noted as adjusted PedsQL) was used to diminish the burden of filling out the entire HRQOL measures twice at the time of the post-test. Items were selected according to the criteria mentioned by Schwartz and Sprangers.[14] The authors selected items that might be remembered well, like pain or fear of injections. Next, items expected to be prevalent shortly after diagnosis were selected, covering the domains of HRQOL. The sum scores of the adjusted PedsQL (aPedsQL) were used for the comparison of pre-, post-, and then-test ratings. Because some domains of HRQOL are more sensitive to recalibration response shift than others,[17] the domains of the aPedsQL were analyzed separately as well. The authors divided the aPedsQL into domains according to the categorization of the original instruments (see Figure 1). For ease of interpretability, the items of the 5-point Likert scale were reversed and converted to a 0-100 scale according to standard procedures so that higher scores indicated better HRQOL. The internal consistency of the aPedsQL was satisfactory (Crohnbach alpha r = 0.74, 0.77, and 0.78 for child report pre-, post-, and then-test; and r = 0.78, 0.87, and 0.76 for parent report pre-, post-, and then-test, respectively). The aPedsQL was representative for the PedsQL instruments, with $R^2 = 0.86$ for child report and $R^2 = 0.88$ for parent report.

Analyses

Changes in HRQOL were examined by comparing the pre- and post-test scores (reported change) and then- and post-test scores (adapted change). To determine whether response shift had occurred, then-tests scores were compared with pretest scores. As the assumptions for normalcy were not met, all comparisons were analyzed using Wilcoxon Signed-Rank Test with an

Physical Functioning
1. I had low energy.
2. I hurt or ached.
3. Food did not taste very good to me.
4. I became sick to my stomach when I thought about medical treatments.

Emotional Functioning
5. I felt afraid or scared.
6. I worried about what would happen to me.
7. I felt angry.
8. I felt sad and blue.
9. I got scared about having needle sticks.

Cognitive Functioning
10. It was hard for me to pay attention to things.
11. I forgot things.

Social Functioning
12. I had problems getting along with other kids.

Communication
13. It was hard for me to ask the doctors and nurses questions.
14. It was hard for me to explain my illness to other people.

Note. Items 3, 4, 9, 13, and 14 are from the PedsQL cancer module. All other items are from PedsQL 4.0 Generic Core Scale.

Figure 1. Domains and items of adjusted PedsQl.

alpha level of 0.05. To test the relationship between child- and parent-report Spearman's correlation coefficient was used.

RESULTS

Change in health status and HRQOL over time

Thirty-seven children (8-17 years), their parents, and 43 parents of children 2-7 years old (80 parents in total) participated in the study (see Table 1). The median parent-reported Play Performance Scale (PPS) values increased ($Z = -3.54$, $p < .001$), indicating that the children's health status improved over the period shortly after diagnosis till three months later. Furthermore, both children and parents reported less symptoms on the Memorial Symptom Assessment Scale (MSAS) at the post-test than at the pretest (child report $Z = 3.23$, $p < .001$; parent report $Z = 4.46$, $p < .001$, see Table 2).

Table 1. Patient characteristics.

Characteristic	Child-report (n=37)		Parent-report (n=80[a])	
	Median	Range	Median	Range
Age of children (years)	14	(8-17)	9	(2-17)
	n (%)		n (%)	
Gender of children				
Female	20 (54.1)		44 (55)	
Diagnosis				
Hematological	12 (32.4)		36 (45)	
Solid tumors	18 (48.6)		26 (32.5)	
Brain tumors	7 (18.9)		18 (22.5)	

[a]Both parents of 37 children ≥ 8years and of 43 children 2-7 years old.

Table 2. Change in scores between pre-tests and post-tests (reported change) and between post-tests and then-tests (adapted change).

	Pretest		Post-test		Then-test		Reported change		Adapted change	
Variable	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	*p*[a]	Effect-size	*p*[a]	Effect-size
HRQL										
Child-report										
Cantril	7	2	8	2	5***	3	.219	-.20	<.001	-.71
aPedsQL	71.43	19.64	76.79	24.11	73.21	17.86	.005	-.46	.010	-.43
Parent-report										
Cantril	6	2	7	2	5*	3	<.001	-.35	<.001	-.44
aPedsQL	60.71	25.30	73.21	23.96	60.71	19.64	.028	-.48	.001	-.43
Health status										
Child-report										
MSAS	11	9	7	10			.001	.53		
Parent-report										
MSAS	13	9	9	9			<.001	.50		
PPS	60	30	80	30			<.001	-.40		

Note. Cantril scores range from 0-10; higher scores indicate higher HRQL. APedsQL (= adjusted PedsQL) scores range from 0-100; higher scores indicate higher HRQL. MSAS (= Memorial Symptom Assessment Scale) scores represent the frequency of symptoms and range from 0-30. PPS (= Lansky Play Performance Scale) scores range from 0-100; higher scores indicate a higher level of play or daily activities. Mdn = median; IQR = inter quartile range. [a] Wilcoxon Signed-Rank Test $*p < .05$, $***p < .001$ Wilcoxon Signed-Rank Test then-test versus pre-test.

The median child report ratings of aPedsQL improved ($Z = -2.81$, $p < .001$). However, the increase of the ratings on Cantril's ladder were not significant ($Z = -1.23$, $p = .219$). The parent-reported scores demonstrated improved HRQOL for both aPedsQL ($Z = -4.33$, $p = .028$) and Cantril's ladder ($Z = -3.10$, $p < .001$). In keeping with the improved health status, HRQOL ratings improved as well.

Response shift

Overall HRQOL

To determine the influence of response shift on the child- and parent-report ratings, the scores of the then-tests and pretests were compared. Wilcoxon Signed-Rank Tests indicated that both children and parents rated the overall HRQOL (Cantril's ladder) retrospectively lower than at the pretest (see Table 2, Figure 2). The median value of the child report pretest was 7 and of the then-test 5 ($Z = -4.40$, $p < .001$). The median value of the parent report pretest was 6 and of the then-test 5 ($Z = -2.52$, $p = .012$). In the response shift literature this difference is interpreted as an *overestimation* of overall HRQOL at the pretest. The improvement in overall HRQOL according to the then-test versus post-test design (adapted change) was significantly greater than based on the pretest versus post-test design both for child- and parent report ($Z = -3.90$, $p < .001$; $Z = -4.17$, $p < .001$) (see Table 2, Figure 2).

Domains of HRQOL

The aPedsQL then-test of both child report and parent report did not differ from the pretest ($Z = -0.57$, $p = .572$ for child report, $Z = -0.08$, $p = .935$ for parent report, see Table 2); thus indicating no response shift for the aPedsQL. Separate analyses of the domains of the aPedsQL demonstrated the largest difference between pre- and then-test in the domain emotional functioning, namely 75.00 at pretest and 69.32 at then-test. However, this difference was not significant ($Z = -1.74$, $p = .081$). Therefore, no response shift could be confirmed for emotional functioning. Then-test ratings and pretest ratings for the other child report domains and for all parent report domains showed no differences.

These results demonstrate that only the ratings of Cantril's ladder were affected by response shift, resulting in an underestimation of the extent of improvement in overall HRQOL between diagnosis and three months post-diagnosis. The aPedsQL ratings were not affected.

Table 3. Comparison child- and parent-report ratings (n=37).

	Child report		Parent report		Difference[a]	Correlation[b]
Variable	Mdn	IQR	Mdn	IQR	*p*	
Cantril's ladder						
Pretest	7	2	6	3	<.001	.48**
Post-test	8	2	7	2	<.001	.70**
Then-test	5	3	5	3	.877	.55**
Response shift	-2	3	-1	4	.001	.55**
PedsQL						
Pretest	71.43	19.64	59.62	26.79	<.001	.64**
Post-test	76.79	24.11	69.64	25.00	.001	.60**

Note. Mdn = median; IQR = inter quartile range
[a] Wilcoxon Signed-Rank Test
[b] Spearman's rho
**$p < .01$

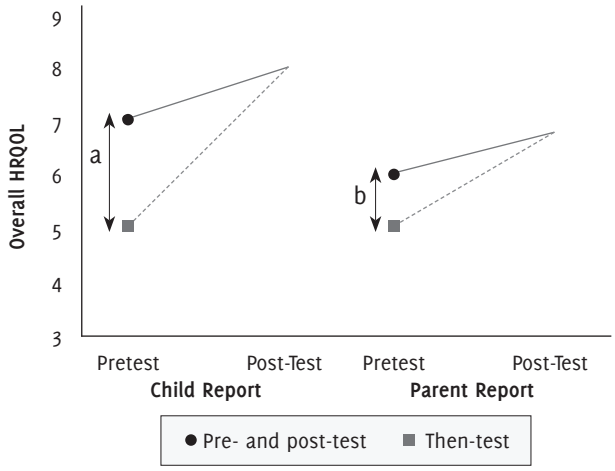

Figure 2. Response shift of overall HRQL of a) child report ratings (n=37) and b) parent report ratings (n=80). Then-test ratings are lower than pretest ratings both for child report (p<.001) and parent report (p<.05). The improvement in overall HRQL according to then- and post-test design is larger than the improvement according to pre- and post-test design (p<.001 both for child- and parent-report). Child report response shift a) is larger than parent report response shift b) (p = .001).
Note. Median values are presented.

Similarities and differences between child- and parent-ratings

For this section, the data of 37 child- and parent-reports were compared pairwise. The pre- and post-test ratings of child- and parent-report of both Cantril's ladder and aPedsQL were positively related: Spearman's rho varied between 0.48 and 0.70 (see Table 3). Parent-reported ratings of HRQOL were lower than child-reported ratings both for Cantril's ladder and for aPedsQL at pre- and post-test.

Because no response shift was found for the PedsQL, further analyses were performed for Cantril's ladder only. The child- and parent-report then-test and response shift of Cantril's ladder were positively related (see Table 3). The Cantril's then-tests did not differ between child- and parent-report. Although at the pretest children and parents rated the overall HRQOL differently, in retrospect their perception of overall HRQOL shortly after diagnosis was nevertheless the same. Comparison of the magnitude of the Cantril's response shift revealed a scale recalibration of -2 points in child report and -1 point in parent report (see Figure 2). The effect-size for child report was -0.74, for parent report -0.30. Children over-estimated the pretest more than parents did ($Z = -3.27$, $p = .001$).

DISCUSSION

This is the first study to explore response shift in the assessment of HRQOL in childhood cancer patients. Our findings are threefold. First, in keeping with an improved health status, HRQOL improved within three months after diagnosis. Second, both child- and parent-report ratings of overall HRQOL were affected by response shift, while the more specific domains of HRQOL were insensitive to response shift. Third, children experienced a greater response shift than parents did. These three results will be discussed in detail below.

1. Because the health status improved within three months after diagnosis, an improved HRQOL was to be expected. However, one measure did not show up significantly. The change in overall HRQOL (Cantril's ladder) was underestimated due to response shift. After taking response shift into account, the improvement of overall HRQOL was profound for both child- and parent-report. That the children's health status and HRQOL improved so quickly in

the three months after diagnosis is a positive finding, despite the fact that they were still in treatment. Only a few studies have assessed HRQOL in this early phase of treatment, and reported either an improvement,[28-30] or no changes in HRQOL.[31] Unfortunately, these studies used different time intervals which make a comparison with our results difficult.

2. The finding of response shift for overall HRQOL is consistent with previous research in adult patients.[9,15,32,33] It corresponds with the then-test hypothesis in the literature stating that adjustment to an improved health status may lead to lower then-test than pretest ratings.[7,19] The pretest overestimation of HRQOL might be explained by children's and parents' coping style to be positive despite the severe illness.[34,35] The fact that the aPedsQL seems to be unresponsive to response shift can be explained by its concreteness. Concrete items are known to be less sensitive to response shift compared to broad domains like overall HRQOL,[15] because a concrete item offers less room for personal interpretation. Other studies using HRQOL instruments at overall and domain level found comparable results.[7,31] The only exception in our findings was the aPedsQL domain of emotional functioning which showed the largest difference between pre- and then-test. However, due to the small sample size statistical significance could not be confirmed. Further research is needed to demonstrate whether child report of emotional functioning is sensitive to response shift. Because the aPedsQL was very representative for the PedsQL instruments, we believe comparable results would have been found when using the total PedsQL. Therefore, for future studies that aim to demonstrate changes in HRQOL the use of the PedsQL instruments is recommended; whereas the use of a global measure like Cantril's ladder is not advisable.

The finding of response shift in parent report is congruent with a study examining response shift in children with middle ear infection. While the health of these children had improved six weeks after surgery, parents rated their child's HRQOL at the then-test more negative than at the pretest.[36] An improved health status resulted in a shift in internal standards when parents realised that the initial HRQOL was worse than perceived at the moment itself. Although recall-bias might explain the differences between pre- and then-test ratings, some facts argue against recall-bias. A study among stroke patients that researched the influence of memory, for instance, found that those with good memory reported the largest response shift.[15] In another study the memory ratings of the pretest turned out to be very similar to the pretest itself, while the then-test ratings differed significantly.[18] Furthermore, it is unlikely that recall-bias would influence the ratings of only the overall HRQOL and not

of both measures of HRQOL. The fact that the then- and pretest ratings of the PedsQL were the same indicates that child and parent were perfectly able to remember the child's condition shortly after diagnosis. Research has demonstrated that children aged 8 years and older could handle a 4-week recall period accurately.[37] In measures assessing life events a 3 months period resulted in valid and reliable outcomes.[38] Moreover, because being diagnosed with cancer is such an overwhelming and daunting experience, we believe children and parents have a vivid memory of this period even after 3 months, thus diminishing recall-bias. Nevertheless, further research on the reliability of recalling a period of 3 month ago is desirable. Another risk factor that should be taken into consideration when using self-report measures is reporting bias. Children and parents might have rated the then-test lower than the pretest, because they feel the situation of the child should have improved as a result of the intensive treatment.

3. We investigated similarities and differences in child and parent reports. Consistent with other studies in childhood cancer patients, parents rated the HRQOL of their children lower than the children themselves did,[39-43] whereas child- and parent-ratings were moderately to strongly and positively related.[4,41-43] The effect-size of the child- or parent-reported response shift differed considerably. According to Cohen's criteria,[44] the effect-size of parent report was small and comparable with mean effect-sizes of overall HRQOL demonstrated in adult patients,[17] while the child report effect-size was large. Hence, the child report of overall HRQOL was more severely biased by response shift than the parent report ratings. The difference in effect-size might be explained by the fact that parents more often have substantial information about the disease and treatment than their child, and are more aware of possible complications and risks. This information and the uncertainty about the prognosis result in lower parent-reported than child-reported ratings of the child's HRQOL at the pretest.[39] Furthermore, children seem to have different response styles than their parents. Children provide more extreme scores and base their judgment on one single example; whereas parents try to give a more balanced rating.[45]

In contrast to the pretest ratings, the then-test ratings of overall HRQOL of children and parents were the same. They had a similar perception of the past HRQOL, probably because they shared the same experience and because the then-test ratings were not affected by adaptation. Comparable results were found in a study among chronically ill patients in which, contrary to the pretest ratings, the patients' then-test ratings corresponded to the proxy-ratings.[2]

Limitations

Some limitations of this study should be noted. First, the final sample consisted of motivated respondents who felt able to participate in the study. Although this phenomenon is not uncommon in survey research, this means that the final sample was not entirely representative of the total population of childhood cancer patients. Another point to acknowledge is that patients had different diagnoses and hence underwent different treatment regimens. However, we believe that neither the heterogeneity of the sample nor the non-response affected the magnitude or direction of response shift, because response shift concerns differences within subjects and not differences between subjects. It would be interesting to test this hypothesis in future research. Second, given the large variation in HRQOL scores, the number of included children was too small to demonstrate changes in overall HRQOL or in the separate domains of HRQOL. Nevertheless, the number was adequate to determine response shift. Third, although the adjusted PedsQL was found to be representative of the PedsQL instruments, it has only been tested in this study. Replication in larger samples is warranted for further validation.

In this study we found an overestimation of overall HRQOL at the pretest. However, it is not known whether overall HRQOL at the post-test was overestimated as well. As a way of coping with the severe illness, children and parents might tend to present the child's quality of life as more positive than it actually is. Unfortunately, performing a then-test at three months after diagnosis is difficult because this time point is difficult to mark. Additional research is needed on coping mechanisms such as repressive adaptation, wishful thinking, and social comparison in childhood cancer patients so as to provide more insight in the mechanisms responsible for response shift. Another important discussion point is which measurement represents HRQOL the best: the actual pre- and post-test, or the retrospective then-test. The authors believe an actual test is preferable. However, researchers should be aware that some self-report measures, including Cantril's ladder, are sensitive to response shift and that measurements of change are biased and may lead to incorrect conclusions. This study demonstrated that the PedsQL instruments, which are frequently used in the assessment of HRQOL in children, were less sensitive to response shift than Cantril's ladder and were able to determine unbiased changes in HRQOL. Because the sample size was relatively small, additional research is warranted to determine how insensitive the PedsQL measures are in larger samples.

In summary, the improvement in overall HRQOL between diagnosis and three

months post-diagnosis was underestimated by response shift. No response shift was demonstrated in the more specific domains of HRQOL. Therefore, the use of the PedsQL is recommended in studies that aim to demonstrate changes in HRQOL.

Implications for nursing practice

Nurses can learn from the current study, that child- and parent-reported ratings of HRQOL can be biased by response shift. As a result, two or more consecutive measurements are not comparable anymore and it becomes difficult to determine, for instance, the impact of treatment or the effect of a nursing intervention. One might wrongly conclude that severity of treatment has no impact on the child's HRQOL or that a nursing intervention does not contribute to HRQOL. Also other subjective scales measuring pain, fatigue, or nausea could be sensitive to response shift.[17] These measures are frequently used in nursing practice and knowledge of response shift helps nurses to better interpret the outcomes of such measures. Besides, the phenomenon of response shift offers an explanation for the high ratings of HRQOL despite severe illness. To surprise of nurses and other health care professionals, children diagnosed with cancer are very positive and optimistic, despite the child being severely ill and experiencing many side effects. They rate their HRQOL higher than nurses would expect. Apparently, they adapt very well to the severe illness. Knowledge of the phenomenon response shift helps nurses to understand and interpret these outcomes.

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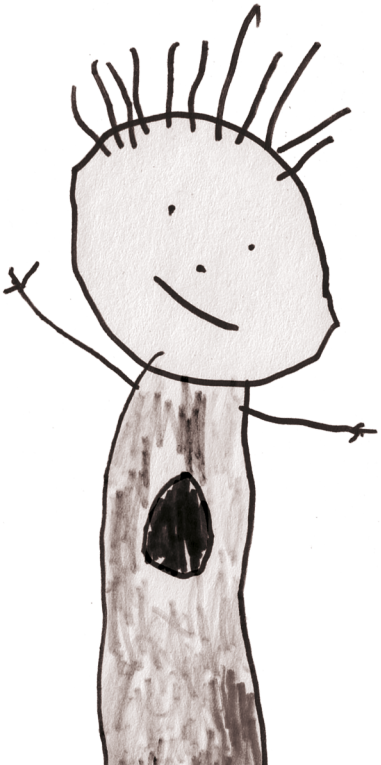
CHAPTER 8

THE IMPACT OF NUTRITIONAL STATUS ON HEALTH-RELATED QUALITY OF LIFE OF CHILDREN WITH CANCER

Aeltsje Brinksma
Robbert Sanderman
Petrie F. Roodbol
Esther Sulkers
Johannes G.M. Burgerhof
Eveline S.J.M. de Bont
Wim J.E. Tissing



Submitted

ABSTRACT

Purpose: Malnutrition in childhood cancer patients has been associated with lower health-related quality of life (HRQOL). However, this association has never actually been tested. Therefore, we aimed to assess the impact of nutritional status on HRQOL of children with cancer.

Patients and methods: In 104 children, aged 2-18 years and diagnosed with hematological, solid, or brain malignancies, nutritional status and HRQOL were assessed at diagnosis and at 3, 6, and 12 months using the child- and parent-report versions of the PedsQL 4.0 Generic scale and the PedsQL 3.0 Cancer Module. Scores on both scales range from 0-100.

Results: Undernourished children (BMI or fat free mass<-2SDS) reported significantly lower PedsQL scores compared with well-nourished children on the domains physical functioning (-13.3), social functioning (-7.0), cancer summary scale (-5.9), and nausea (-14.7). Overnourished children (BMI or fat mass>2SDS) reported lower scores on emotional (-8.0) and cognitive functioning (-9.2) and on the cancer summary scale (-6.6); whereas parent-report scores were lower on social functioning (-7.5). Weight loss (>0.5 SDS) was associated with lower scores on physical functioning (-13.9 child-report and -10.7 parent-report), emotional (-7.4) and social functioning (-6.0) (child-report), pain (-11.6), and nausea (-7.8) (parent-report). Parents reported worse social functioning and more pain in children with weight gain (>0.5 SDS).

Conclusion: Undernutrition and weight loss were associated with worse physical and social functioning; whereas overnutrition and weight gain affected the emotional and social domain of HRQOL. Measures that improve nutritional status will contribute to enhanced health outcomes in children treated for cancer.

INTRODUCTION

A poor nutritional status during treatment for childhood cancer not only has substantial clinical implications, but also adversely affects a child's quality of life. Both undernutrition and overnutrition are common in children treated for cancer and can lead to more complications, higher relapse rates, and lower survival rates.[1-3] Metabolic alterations, reduced intake, and increased losses, due to vomiting and diarrhea, can result in weight loss and undernutrition.[4] At the same time, weight gain and alterations in body composition have frequently been reported in this particular patient group.[5-7]

During the last two decades, improved survival rates have resulted in increased emphasis on children's personal needs. As a result, health-related quality of life (HRQOL) of children with cancer has become a critical issue in clinical practice. The use of intensive treatments combining chemotherapy, surgery, and radiation causes many side effects which negatively affect children's HRQOL.[8] Generally, it is assumed that HRQOL in undernourished patients is lower compared with well-nourished patients[9] and that improvement of nutritional status will contribute to a better HRQOL. However, this association between nutritional status and HRQOL in children treated for cancer has never been tested.

In adult cancer patients, undernutrition and weight loss have been linked with lower scores on all domains of HRQOL.[10-12] Furthermore, overnutrition in healthy children has been linked to lower HRQOL scores as well. Whether overnutrition has negative consequences for HRQOL in children treated for cancer is unknown.

The current study is the first to explore the association between nutritional status and HRQOL in children treated for cancer. HRQOL in children is preferably measured using both child self-report and parent proxy-report.[13,14] Children and parents do not necessarily have similar views on the impact of the disease.[15] Nevertheless, both reports provide valuable and complementary information towards a better understanding of the child's HRQOL. The objective of this study is to quantify the impact of undernutrition, overnutrition, weight loss and weight gain on HRQOL in a heterogeneous sample of childhood cancer patients during the first year after diagnosis.

METHODS

Participants

Participants were children between 2-<18 years of age who were diagnosed with cancer between September 2007 and December 2009 and who were willing to participate in the PeCanNut (Pediatric Cancer and Nutrition) study[5] of the Pediatric Oncology Department of the University Medical Center Groningen (UMCG). Eligible patients were able to understand the Dutch language, received curative treatment, and were aged ≥ 5 years for child-report of HRQOL or were aged ≥2 years for parent proxy-report. A total of 128 patients met the inclusion criteria, of which 109 were aged ≥5 years. Reasons for attrition are presented in Figure 1. Ethical approval was obtained from the Medical Ethics Committee of the UMCG, and both parents and children aged ≥ 12 years gave their written consent.

Procedure

Measurements were taken at diagnosis, and at 3, 6, and 12 months after diagnosis. The follow-up measurements were taken between courses of chemotherapy to make participation more acceptable to patients.

Measures

Nutritional status

Weight, height and body mass index (BMI) were assessed and expressed as standard deviation scores (SDS) calculated from Dutch reference standards.[16,17] Furthermore, fat free mass (FFM) and fat mass (FM) were based on bioelectrical impedance analyses (BIA) using a 50 kHz frequency BIA (BIA 101, Akern, Italy) and were expressed as SDS using Dutch reference values.[18] Details regarding measurements have been published previously.[5]

Undernutrition was defined as BMI<-2SDS or FFM<-2SDS, and overnutrition as BMI>2SDS or FM>2SDS. Children with both FFM<-2SDS and FM>2SDS and children aged <4 years were solely classified based on BMI. Changes in weight following the previous measurement were expressed in changes in weight-for-age (WFA) SDS and as such controlled for normal growth during the study period. Relevant weight loss or weight gain was defined as >0.5 SDS WFA change. A 0.5 SDS increase or decrease corresponded to a weight change of up to 5%. In children with cancer, weight loss >5% was found to be associated with increased infection rates (E. Loeffen 2014). In adult patients, 5% weight loss is also used as criterion for critical weight loss.[19]

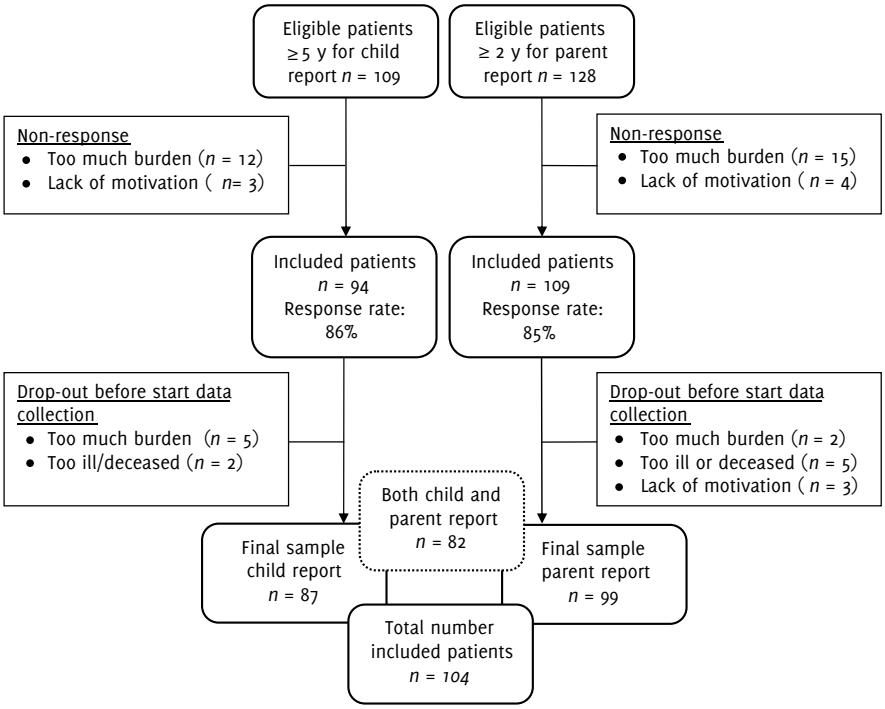


Figure 1. Flowchart patient inclusion for child and parent report

Health-related quality of life

The PedsQL measures are comprised of parallel child self-report formats (ages 5 and older) and parent proxy-report formats (ages 2 and older). The PedsQL 4.0 Generic Core Scale[20,21] is a 23-item, multidimensional scale designed to measure generic HRQOL and includes 4 subscales: physical, emotional, social, and school functioning. The subscales can be summed into total scale scores, and psycho-social summary scores (composed of emotional, social, and school subscales).

The PedsQL Cancer Module[22] is a 27-item scale developed to measure cancer specific HRQOL in children and includes 8 subscales: pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication. A total scale score and scores for the subscales pain and hurt, nausea, cognitive problems, and perceived physical appearance were calculated. These subscales were considered to be relevant in relation to nutritional status.

To improve interpretability of the scores, the items of the 5-point Likert scale were reversed and converted to a 0-100 scale following standard procedures[23] so that higher scores indicated better HRQOL. Both PedsQL instruments have high levels of reliability and validity.[20-22,24]

Demographic and medical characteristics

The following patient characteristics were included in the analyses: age, gender, socioeconomic status (SES), type of malignancy, treatment severity, and treatment phase. Treatment severity was measured with the Intensity of Treatment Rating Scale (ITR-3).[25] Treatment phase was expressed as being on-active treatment or off- treatment. Education level of the father was included as a proxy for SES and stratified into three categories (low vocational education; intermediate vocational or general secondary education; higher professional or university education).

Data analysis and statistics

Prevalence rates of undernutrition, overnutrition and the number of patients with relevant weight loss or weight gain were calculated. The course of the PedsQL scales over time was estimated using unconditional growth models (Mixed models in SPSS). Paired t-tests were performed to compare child-report scores and parent-report scores.

In order to develop a powerful model and to prevent multiple testing by separate analyses at every measurement time, the association between undernutrition, overnutrition, weight changes and HRQOL was analyzed using multilevel analyses (Mixed models). We developed two series of predictive models of HRQOL as a function of time: one including categories undernourished, overnourished, and well-nourished as predictors, and one including weight loss, weight gain, and stable weight as predictors. Nutritional status was tested both for main effects and interaction effects with time. Time was expressed as time in months. The well-nourished and stable weight groups were used as reference categories. The demographic factors and medical characteristics were included as co-variables. These were first univariately tested for their association with either nutritional status or HRQOL by adding the variables to the unconditional growth model. Based on likelihood ratio tests, the co-variables were selected for inclusion in the multivariate multilevel analyses. In the analyses with weight change as a predictor, BMI SDS at diagnosis was included to control for the difference in impact of weight changes in lean or obese children. To compare the outcomes of the conditional growth models

of child self-report and parent proxy-report HRQOL, multilevel analyses of parent-report HRQOL were performed twice: once for all parent-report data (age children 2-18 years) and once for those cases with available child-report data (age children 5-18 years). All cases, including cases with missing data, were included for analyses. Analyses were performed using IBM SPSS Statistics 20. Statistical significance was accepted at the 5% level.

RESULTS

Characteristics of the cohort

In total, 104 patients (aged 2-18 years) diagnosed with hematological (43%), solid (33%), or brain malignancies (24%) participated in the study (Table 1). Of 87 patients, child-report data of the PedsQL were available, and of 99 patients parent-report data were available at any given measurement time (Figure 1). The majority of the patients received moderately intensive or very intensive treatment.

Descriptives nutritional status and health-related quality of life

Nutritional status

Percentage undernourished patients (BMI or FFM<-2SDS) decreased from 19% at diagnosis to 10% after 12 months; whereas for overnourished patients (BMI or FM>2SDS) these figures were 9% to 18%, respectively. When using only BMI to define nutritional status, 8% to 1% was undernourished and 5% to 11% was overnourished at diagnosis and 12 months respectively. Twenty-eight percent of the patients experienced weight loss (>0.5 SDS WFA); whereas 37% gained more than 0.5 SDS WFA in the measurement period. On average, 15% (range 0%-36%) of the patients were classified as malnourished in both classifications; they were either undernourished and experienced >0.5 SDS weight loss or gain, or overnourished and experienced >0.5 SDS weight loss or gain. Details regarding the nutritional status of this cohort have been presented more extensively elsewhere.[5]

Health-related quality of life

HRQOL improved during the study period. PedsQL total child-report improved from 67.4 (SD18.2) at diagnosis to 77.6 (SD 15.5) after 12 months (estimate slope .90 per month, 95% CI .59; 1.21, P< .001). PedsQL total

Table 1. Patient characteristics (n=104)

Characteristic		
Age median (range)	9.0	(2.0-17.7)
	n	**(%)**
Gender: female	56	(54)
Diagnosis:		
Hematological	45	(43)
Leukemia	33	(32)
ALL	28	(27)
AML	5	(5)
Lymphoma	12	(12)
Solid tumors	34	(33)
Neuroblastoma	7	(7)
Wilms tumors	5	(5)
Bone	8	(8)
Solid other	14	(14)
Brain tumors	25	(24)
Medullo- and ependymoblastoma	6	(6)
Astrocytoma/glioma	9	(9)
Craniopharyngioma	4	(4)
Other	6	(6)
Intensity of Treatment Rating (ITR)		
Least intensive	6	(6)
Moderate intensive	51	(49)
Very intensive	43	(41)
Most intensive	4	(4)
Education level father[a]		
Low vocational education	26	(25)
Intermediate vocational/general secondary education	45	(43)
Higher professional/university education	25	(24)

[a] Education level of the father was used as a proxy for socioeconomic status. For 8 respondents data about education level were missing.

parent-report improved from 59.1 to 73.7 (estimate slope 1.12 per month, 95% CI .74; 1.51, P<.001). Scores on PedsQL Cancer Module improved from 75.0 (SD 15.5) to 82.1 (SD12.0) (estimate slope .59 per month, 95% CI .33; .86, P<.001) and from 71.9 (SD14.3) to 82.0 (SD14.7) (estimate slope .74 per month 95% CI .48; 1.01, P<.001) for child- and parent-report respectively. Parent proxy-report scores were lower than child-report scores on total PedsQL at all measurement times (t=2.41 to 4.08, all *P* values < 0.05) and on the PedsQL Cancer Module at diagnosis and at 3 months (t=2.34, df=74, P = 0.022 and t=2.01, df=67, P = 0.041 respectively).

Co-variable testing

Univariate testing showed that type of malignancy and phase of treatment were related to nutritional status: children with brain malignancies had higher FM and lower FFM than children with hematological and solid malignancies, and children on-treatment had lower FFM than children off-treatment. Age, gender, type of malignancy, and phase of treatment were associated with HRQOL: older children, girls, children with brain malignancies, and children on-treatment reported lower HRQOL on one or more of the PedsQL summary scales or subscales. No relationship was found between SES or treatment intensity and HRQOL. Age, gender, type of malignancy, and phase of treatment were therefore included in the multilevel analyses to test whether differences in PedsQL scores were related to nutritional status or to one of the co-variables.

Association between nutritional status and HRQOL

Multilevel analyses showed no interaction between nutritional status and time; thus the trajectories of change in HRQOL over time were not significantly different for under-, over-, and well-nourished children (Figures 2a-2d, 3a-3d) and for children with weight loss, weight gain and stable weight. Therefore, only main effects are reported. The results of the analyses of all parent-report data (ages 2-18 y) and parent-report data of children 5-18 years were similar. Therefore, the results of the analyses of all parent-report data are presented.

Undernutrition

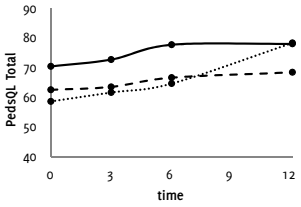
Undernourished patients reported significantly lower total PedsQL scores (-6.0, P=0.003) (child-report) than well-nourished patients (Table 2, figure 2a,). The differences were reflected in both physical and social functioning: undernourished patients scored 13.3 (P=0.006) and 7.0 (P=0.014) points

Table 2. Association between nutritional status and HRQOL **child-report** (n=87) based on two separate multilevel analyses.[a] The 1st and 2nd estimate represent the differences in PedsQL scores of under- or overnourished children compared with well-nourished children (reference group). The 3rd and 4th estimate represent the differences in PedsQL scores of children with weight loss or weight gain compared with children with stable weight (reference group).

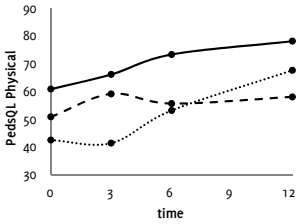
	Reference group: well-nourished						**Reference group: stable weight**					
	Undernourished[b]			Overnourished[c]			Weight loss[d]			Weight gain[d]		
	Estimate	95%CI	*P*	Estimate	95%CI	*P*	Estimate	95%CI	*P*	Estimate	95%CI	*P*
PedsTotal	**-6.0**	-11.6; -.5	.003	-6.0	-12.3; .4	.065	**-7.2**	-12.4; -1.9	.008	-.6	-5.2; 4.1	.812
Peds Physical	**-13.3**	-22.9; -3.8	.006	-7.9	-18.7; 2.9	.151	**-13.9**	-23.3; -4.6	.004	1.5	-6.7; 9.7	.724
Peds Psycho-social	-2.4	-7.1; 2.3	.319	**-5.4**	-10.8; -.1	.046	-4.2	-8.6; .2	.062	-2.6	-6.5; 1.3	.186
Peds Emotional	3.3	-3.1; 9.9	.303	**-8.0**	-15.2; -.8	.029	**-7.4**	-14.2; -.7	.032	-5.3	-11.2; .7	.083
Peds Social	**-7.0**	-12.6; -1.4	.014	-6.1	-12.4; .1	.054	**-6.0**	-11.1; -1.0	.020	-2.4	-6.8; 2.1	.296
Peds School	-2.9	-10.6; 4.9	.467	-4.0	-12.6; 4.5	.354	.27	-7.7; 8.3	.947	-1.4	-8.5; 5.7	.694
Peds Cancer	**-5.9**	-10.6; -1.3	.013	**-6.6**	-11.8; -1.4	.013	-.9	-5.5; 3.7	.701	1.7	-2.3; 5.8	.397
Pain	-1.4	-11.4; 8.7	.788	-4.6	-15.5; 6.2	.401	-7.8	-19.0; 3.4	.170	4.0	-5.9; 13.9	.423
Nausea	**-14.7**	-22.7; -6.6	.000	-5.5	-14.3; 3.4	.225	1.4	-6.9; 9.7	.738	5.7	-1.6; 13.1	.126
Cognition	-4.5	-10.9; 1.9	.164	**-9.2**	-16.6; -1.9	.014	-.4	-6.7; 6.0	.913	-5.3	-11.0; .3	.064
Appearance	-.1	-8.0; 7.7	.972	-5.6	-14.4; 3.2	.209	1.9	-6.0; 9.8	.632	1.9	-5.1; 8.8	.596

[a] Dependent variable PedsQL, independent variable nutritional status divided into 3 groups: undernourished, overnourished, and well-nourished; or weight loss, weight gain, stable weight. Reference category: well-nourished or stable weight. Included co-variables are: age, gender, type of malignancy, and phase of treatment.
[b] Based on BMI < -2SDS or FFM < -2 SDS.
[c] Based on BMI > 2SDS or FM >2 SDS.
[d] Weight loss or weight gain > 0.5 SDS.
Abbreviation: CI, confidence interval.

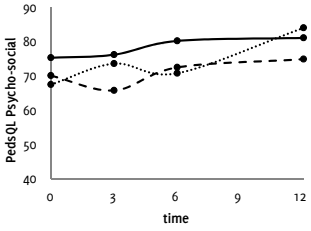
Figure 2.



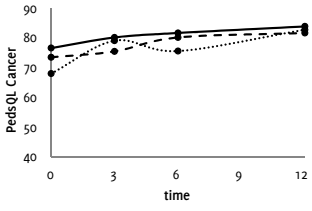
2a. PedsQL Total child-report



2b. PedsQL Physical child-report

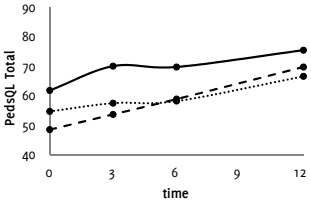


2c. PedsQL Psycho-social child-report

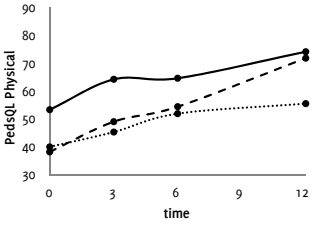


2d. PedsQL Cancer child-report

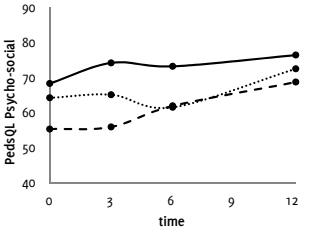
Figure 3.



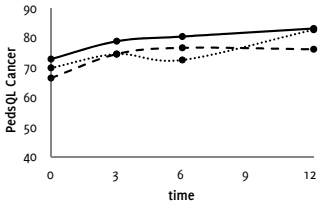
3a. PedsQL Total parent-report



3b. PedsQL Physical parent-report



3c. PedsQL Psycho-social parent-report



3d. PedsQL Cancer parent-report

well-nourished
undernourished
overnourished

Figure 2 and 3 represent the trajectories of the PedsQL scores, based on child- or parent-report, for well-nourished, undernourished (BMI or FFM < -2SDS), and overnourished (BMI or FM > 2 SDS) children. The composition of the groups under-, over-, and well-nourished varied per measurement time: e.g. a patient could be in the undernourished group at diagnosis and in the well-nourished group at 3 months after diagnosis.

Table 3. Association between nutritional status and HRQOL **parent-report** (n=99) based on two separate multilevel analyses.[a] The 1st and 2nd estimate represent the differences in PedsQL scores of under- or overnourished children compared with well-nourished children (reference group). The 3rd and 4th estimate represent the differences in PedsQL scores of children with weight loss or weight gain compared with children with stable weight (reference group).

	Reference group: well-nourished						**Reference group: stable weight**					
	Undernourished[b]			Overnourished[c]			Weight loss[d]			Weight gain[d]		
	Estimate	95%CI	*P*	Estimate	95%CI	*P*	Estimate	95%CI	*P*	Estimate	95%CI	*P*
PedsTotal	-3.0	-9.6; 3.6	.372	-6.0	-13.7; 1.6	.122	**-8.3**	-15.0; -1.5	.016	-3.7	-10.0; 2.6	.252
Peds Physical	-8.2	-18.1; 1.7	.104	-4.9	-16.3; 6.6	.402	**-10.7**	-20.6; -.8	.034	-4.9	-14.0; 4.3	.297
Peds Psycho-social	-.8	-6.6; 5.0	.778	**-7.5**	-14.3; -.8	.028	-5.2	-11.4; .93	.096	-4.4	-10.0; 1.3	.130
Peds Emotional	.3	-7.0; 7.7	.927	-6.5	-15.2; 2.1	.135	-4.1	-11.4; 3.3	.275	-2.5	-9.3; 4.3	.470
Peds Social	-3.6	-9.7; 2.6	.253	**-7.5**	-14.7; -.2	.043	-6.1	-12.3; .1	.052	**-6.0**	-11.7; -.3	.040
Peds School	1.9	-8.1; 12.0	.708	-8.2	-19.4; 3.0	.150	-10.2	-20.8; .5	.061	-3.7	-13.3; 5.9	.449
Peds Cancer	-.0	-4.9; 4.8	.988	-4.2	-10.1; 1.6	.156	-3.1	-7.9; 1.7	.205	-1.6	-6.0; 2.7	.463
Pain	3.8	-5.6; 13.3	.426	-9.4	-20.3; 1.6	.093	**-11.6**	-21.4; -1.8	.021	**-9.2**	-18.4; -.0	.049
Nausea	-6.4	-14.2; 1.4	.108	-4.1	-13.4; 5.1	.376	**-7.8**	-15.3; -.3	.041	3.8	-3.2; 10.9	.287
Cognition	2.7	-4.7; 10.0	.477	-5.4	-14.3; 3.4	.227	.9	-6.6; 8.5	.811	-6.6	-13.5; .3	.060
Appearance	-4.6	-12.4; 3.1	.239	-8.5	-17.6; .5	.065	-2.5	-9.8; 4.7	.493	-3.1	-9.8; 3.5	.352

[a] Dependent variable PedsQL, independent variable nutritional status divided into 3 groups: undernourished, overnourished, and well-nourished; or weight loss, weight gain, stable weight. Reference category: well-nourished or stable weight. Included co-variables are: age, gender, type of malignancy, and phase of treatment.
[b] Based on BMI< -2SDS or FFM < -2 SDS.
[c] Based on BMI> 2SDS or FM > 2 SDS.
[d] Weight loss or weight gain > 0.5 SDS.
Abbreviation: CI, confidence interval.

lower respectively. Undernourished patients also reported lower scores on the PedsQL Cancer Module (-5.9, P=0.013) and the subscale nausea (-14.7, P<0.001). Parent report revealed no significant differences between under- and well-nourished patients on either one of the PedsQL scales (Table 3).

Overnutrition

Overnourished patients scored 5.4 points lower (P=0.046) on the psycho-social summary scale (child-report) than well-nourished patients (Table 2, figure 2c). This difference was reflected in both emotional functioning (-8.0, P=0.029) and social functioning (-6.1, P=0.054). Overnourished patients reported lower scores on the PedsQL Cancer Module (-6.6, P=0.013) and the subscale cognitive problems (-9.2, P=0.014). Parents of the overnourished patients scored lower on the psycho-social summary scale (-7.5, P=0.028) and on social functioning (-7.5, P=0.043) (Table 3). Overnourished patients also scored lower on physical functioning; however, the differences were not statistically significant.

Weight loss

Children with weight loss (>0.5 SDS) scored 7.2 points lower (P=0.008) on total PedsQL (child-report) compared with children with stable weight (Table 2). They scored lower on physical (-13.9, P=0.004), emotional (-7.4, P=0.032), and social functioning (-6.0, P=0.020) (Table 2). No differences were found for the PedsQL Cancer Module. Parent reports were lower for PedsQL total (-8.3, P=0.016) and for physical functioning (-10.7, P=0.034) (Table 3). Furthermore, parents reported more pain (-11.6, P=0.021) and nausea (-7.8, P=0.041) in children with weight loss.

Weight gain

Children with weight gain (>0.5 SDS) had similar PedsQL scores on all scales compared with children with stable weight (child-report). Parent-reports of children with weight gain were 6.0 points lower (P=0.040) on social functioning and 9.2 points lower (P=0.049) on pain.

DISCUSSION

This is the first study to explore the association between nutritional status and HRQOL in children treated for cancer. The results of the Pecannut study indicate that both undernourished children and overnourished children experienced worse HRQOL compared with well-nourished children. Significant weight loss and weight gain also contributed to worse HRQOL. To date, several studies have demonstrated worse HRQOL in undernourished adult cancer patients.[11,12,26-28] However, to our best knowledge, the association between overnutrition and HRQOL has never been studied in cancer patients (adults or children).

Previous studies have shown that children treated for cancer have the lowest HRQOL when compared with healthy children or children with other diseases.[20,29-31] The current study, however, demonstrates that under- and overnourished patients had the poorest HRQOL of all cancer patients. When examining the domains of HRQOL, impaired physical functioning was most prevalent in undernourished children and children with weight loss. It is well-known that undernutrition and weight loss are associated with loss of muscle mass and muscle weakness, resulting in fatigue.[32] Hence, undernourished children lacked the energy and muscle strength to participate in physical activities. In addition, undernourished children reported more side effects of treatment: they had lower scores on the PedsQL Cancer Module, and experienced more pain and nausea. Pain and nausea have also been associated with fatigue,[33] which impairs children's ability to cope with side effects of treatment. Furthermore, tolerance for (toxicity of) chemotherapy may be less in undernourished patients,[4] resulting in more side effects. Finally, undernourished children reported impaired social functioning. This finding can be explained by the pain, nausea, and fatigue these children experience, which impairs their ability to fully participate in physical and social activities with peers.

Compared with well-nourished children, overnourished children and children with weight gain reported worse functioning in the psycho-social domain, in particular in emotional and cognitive functioning; whereas parent-report scores were lower on social functioning. This implies that overnourished children "did not feel well": they were more vulnerable to feelings of fear, sadness, and anger; experienced more difficulties in the interaction with other children; and experienced more difficulties in performing cognitive

tasks than well-nourished children with cancer. A literature review[34] on HRQOL in healthy obese children and adolescents found that overweight had a negative impact on social and emotional functioning. Thus, the negative consequences of overweight in healthy children also apply to children with cancer. Contrary to obese healthy children, overnourished cancer patients did not experience worse physical functioning than well-nourished patients. It is likely that the impact of cancer and its intensive treatment on the children's physical functioning exceeded the impact of differences in nutritional status. Notably, overnourished children scored lower on cognitive functioning; whereas undernutrition is expected to be associated with lower performance on cognitive tasks.[35]

An additional finding of this study was that children and parents reported differently on the impact of nutritional status on HRQOL. The most significant difference between child- and parent-report concerned the HRQOL of undernourished children: children reported significant impairments in several domains of HRQOL; whereas parent-report ratings failed to demonstrate differences between under- and well-nourished children. The fact that child- and parent-report had different outcomes does not reflect the lack of validity of either child- or parent-report, but rather reflects the different perspectives of children and parents on the child's HRQOL.[36] For example, children's perceptions are based on their subjective personal experiences with regard to symptoms such as fatigue, nausea, and pain. Children suffer from their undernourishment at first hand; whereas parents' view of their child's HRQOL is more indirect and relies on their external observations and on communication with the child.[37]

Consistent with the literature,[14,37,38] in the current study parent HRQOL ratings were lower than children's ratings. Parents are often more well-informed about treatment and prognosis, and they perceive cancer to have more negative consequences than children themselves. Moreover, their views may be influenced by the burden of care-giving, their own well-being, and other concerns.[14] Nevertheless, the perspectives of both children and parents complement each other and increase our understanding of the association between nutritional status and the child's HRQOL.

Despite the fact that the current study concerned one of the largest prospective cohorts of children treated for cancer, the number of under- or overnourished patients at every single measurement time was relatively small. Therefore, to improve statistical power multilevel analyses were performed including all 4 measurement times.

This study demonstrated that during treatment HRQOL in undernourished patients and patients with weight loss is significantly lower than in well-nourished patients. However, overnourished patients and patients with weigh gain were also more vulnerable to negative feelings and performed worse in several domains of HRQOL. These findings stress the importance of adequate nutritional care during treatment. Nutritional care as component of supportive care not only contributes to fewer complications and higher survival rates, but also contributes to better HRQOL outcomes in children treated for cancer. Finally, this study shows the added value of hearing both the children's and the parents' voices towards a better understanding of children's HRQOL.

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CHAPTER 9

SUMMARY AND GENERAL DISCUSSION: FINDINGS, CLINICAL IMPLICATIONS, AND FUTURE RESEARCH

INTRODUCTION

Florence Nightingale, one of the founders of nursing, was the first to demonstrate the added value of systematic data collection and statistical analysis. By providing diagrams of mortality rates of English military hospitals during the Crimean War (1853-1856), she convinced the Ministry of Defense to introduce hygienic measures to prevent diffusion of cholera and typhus.1 Florence Nightingale was, in fact, the first to demonstrate the added value of nursing research. Her approach to obtain simple data such as weight, vital signs, symptoms, and impairments in functioning is very valuable because these data can play an important role in improving patient care.

When a child is diagnosed with cancer its food intake and nutritional status is at risk. Many children have a decreased nutrient intake because they feel ill or because their taste is altered and they dislike many foods. Other children have an increased appetite and can't stop eating because of the dexamethasone. Some children lose weight and become undernourished; whereas others gain weight and become obese. A variety of problems regarding food intake and nutritional status occurs. The Pecannut study aimed to identify these problems by registration of, among others, weight and food intake. The study determined the course of nutritional status, the factors related to nutritional status, and the consequences of malnutrition.

In the next sections the main findings of the Pecannut study will be summarized and discussed, implications for clinical practice will be presented, and this chapter will end with directions for future research.

FINDINGS: WHAT IS KNOWN

The results of the systematic review reveal that four decades of research have still not resulted in a definition of reliable prevalence rates of malnutrition (**Chapter 2**). The limited number of studies, particularly in children with solid and brain malignancies; the small samples sizes; and the use of different criteria to define malnutrition mean that prevalence rates can only be estimated. Furthermore, because the number of longitudinal studies is limited, little is known about the timing and onset of weight loss or weight gain.

In addition, it is not known whether energy deficiency or inflammation contribute to malnutrition during treatment, and evidence for an increased metabolic rate is inconclusive (Chapter 2). Although energy intake has been

found to be lower than recommended daily allowances (RDA), the impact of inadequate intake on nutritional status has not yet been tested (Chapter 2). Moreover, low levels of physical activity may have compensated for low energy intake, thus preventing energy deficiency. Finally, very little research has explored the process of inflammation in relation to cachexia in children with cancer. The presence of increased inflammatory markers at diagnosis seems likely. However, a relationship with weight loss has not been found.
Based on the systematic review the following points seem to be essential:

- Longitudinal studies assessing nutritional status, weight loss, and body composition in heterogeneous sample of childhood cancer patients are needed;
- Well-designed studies are needed to establish the energy needs of childhood cancer patients and to evaluate the consequences of energy deficiency on nutritional status;
- More research is needed on the presence of inflammatory processes and the impact of inflammation on nutritional status.
- The first two points are addressed in the Pecannut study.

FINDINGS: WHAT IS NEW

Prevalence of malnutrition

Based on actual data of weight and height, 2%, 4%, and 7% of the children were undernourished at diagnosis according to weight-for-age (WFA), height-for-age (HFA), and weight-for-height (WFH) below -2 standard deviation score (SDS) respectively (**Chapter 3**). However, compared with their growth charts another 20-24% of the children lost more than 0.5 SDS in WFA, HFA, and WFH. In fact, children's real nutritional status at diagnosis was worse than the actual data of weight and height indicated and more children were undernourished.
During the first 12 months after diagnosis, weight, body mass index (BMI), and fat mass (FM) increased (**Chapter 4**). In patients with brain malignancies, increase of BMI started immediately after diagnosis; whereas BMI in patients with hematological and solid malignancies initially decreased, only to increase later on during treatment. Prevalence rates of overnutrition based on BMI >2 SDS doubled from 5% at diagnosis to 10% after 12 months; whereas prevalence rates of undernutrition based on BMI <-2SDS decreased

from 8% at diagnosis to 2% after 12 months. When FM and fat free mass (FFM) were included to define the nutritional status, even more children were under- or overnourished (Chapter 4). Contrary to high FM, FFM was low at diagnosis and remained low during the study period; approximately 17% of the patients were undernourished on the basis of low FFM. Patients with brain malignancies had the lowest FFM and the highest FM. Patterns of increase in FM did not differ between patients with hematological, solid, or brain malignancies.

In addition to low values of BMI and FFM, significant weight loss (>0.5 SDS) was prevalent in 28% of the patients during the first 3 months, particularly in patients with hematological and solid malignancies. As we demonstrated in Chapter 6, these patients had a higher risk of infections.

In sum, our study demonstrates that the issues regarding nutritional status in children treated for cancer are complicated. This patient group is not only confronted with undernutrition, weight loss, and a low FFM, but also with overnutrition and high fat mass. The current results indicate that in industrialized countries the focus on undernutrition might very well lead to neglect of overnutrition. The alterations in body size and body composition during treatment are of serious concern in both the short and the long term; in fact, the literature reports increased levels of FM and BMI even years after cessation of therapy in survivors of childhood cancer.[2,3]

Factors related to malnutrition

Dietary intake

Dietary intake is one of the main factors contributing to nutritional status. Inadequate intake is associated with weight loss; whereas excess intake is associated with weight gain. In **Chapter 5**, these associations were studied in children treated for cancer. The results show that children's energy intake was, on average, 105% of the energy requirements, which were calculated using Schofield's equation.[4,5] In contrast, children's intake was 80% of RDA and 84% of intake in healthy controls. Thus, while the children's energy intake broadly matched the calculated energy requirements, it was inadequate compared with the last two norms. The gain in weight, BMI, and FM, as described in Chapter 4, suggests that energy intake was sufficient to meet or even exceeded patients' requirements. These results imply that the norms of RDA and intake in healthy controls are too high for children treated for cancer. Apparently, childhood cancer patients require less energy than RDA and less energy than healthy children.

Energy intake was also negatively associated with nutritional status. Lean children with low body weight had higher intakes than children with high fat mass and high body weight. An obvious explanation for this inverse relation is that lean children were more often fed by tube feeding and that this type of feeding increased their intake. Another possible explanation might be found in the timing of the assessment which was between the courses of therapy and not during therapy. Presumably, patients experienced alternating periods of poor and good intake; whereas we just registered the good periods. The higher intakes in lean children, as registered in the periods between the courses of therapy, might be a compensation for their lower intake during prior periods.
Another finding was that protein intake was almost twice the recommend allowances and the individual requirements. Unfortunately, the high protein intake did not have a beneficial effect on FFM. As reported in Chapter 4, FFM was low at the beginning of treatment and remained low. This finding could be explained by the fact that the protein requirements needed to improve FFM may be higher than the current recommendations. In addition, a certain level of physical activity is necessary to improve FFM and children treated for cancer are known to be less active because of the side effects of their treatment regimens.

Patient characteristics, treatment related factors, and physical activity

In addition to energy intake, patient characteristics, treatment related factors, and level of physical activity were tested for their association with changes in nutritional status (**Chapter 4**). Type of malignancy was the only factor related to weight loss in the beginning of treatment; patients with hematological and solid malignancies first lost weight; whereas patients with brain malignancies gained weight from the beginning of treatment. The increase in BMI during the first 3 months was related to initial nutritional status and tube feeding. The faster increase in BMI in children who were poorly nourished at the time of diagnosis may be seen as catch-up growth. As we demonstrated in Chapter 3, weight and height at diagnosis were lower than estimated weight and height based on children's growth curves. Catch-up growth may be interpreted as beneficial weight gain. In addition, children receiving tube feeding demonstrated more weight gain than children without tube feeding. The general aim of tube feeding is to maintain or to improve nutritional status. However, it is difficult to draw the line between catch-up growth and overfeeding. Given that weight

continuously increased during the 12 months after diagnosis, and given that z-scores of weight during treatment (Chapter 4) were higher than the predicted values of weight based on children's growth curves (Chapter 3), we conclude that weight gain was partly due to catch-up growth and partly due to overfeeding by tube feeding. The results of Chapter 5 confirm that average energy intake was more than patients' requirements and that energy intake in tube fed patients was 10% higher than in children without tube feeding. In order to prevent and treat undernutrition, children were fed too aggressively, resulting in overweight.

Contrary to findings in other studies, we did not find an association between increase in BMI and age, gender, or parental BMI,[6-8] nor did we find an association between increase in BMI and treatment intensity, symptoms, or physical activity. All these factors were interrelated to tube feeding, making tube feeding the main related factor for weight gain. Treatment with corticosteroids is often linked to increase in BMI, because energy intake increases during corticosteroid treatment. [9,10] However, studies testing the impact of corticosteroids on BMI have shown contradictory results.[7,11] In our study, an association with corticosteroid use was not found.

Low physical activity was found to be the main factor contributing to increase in %FM. This finding is congruent with research in healthy children and adolescents.[12] Similar to increase in BMI, high energy intake or treatment with corticosteroids are assumed to cause increase in FM.[13-15]Again, similar to the BMI results, such a relationship was not found in our study. Physical activity was found to be the only contributing factor to increase in %FM. Children treated for cancer have lower levels of physical activity,[16] but their energy intake is adequate or even higher than adequate. Thus, it can be concluded that increase in weight was caused by increase in FM.

In sum, energy intake is assumed to be the main factor affecting children's nutritional status. However, the results of the Pecannut study revealed that in clinical practice associations between energy intake and nutritional status are complex. Not energy intake but tube feeding, representing the children with the highest intake and the lowest scores for physical activity, contributed to increase in BMI. The positive energy balance and the low level of physical activity resulted in increase of FM. In fact, the same mechanisms that cause obesity in healthy children seem to play a predominant role in the development of overnutrition in children treated for cancer.

Consequences of malnutrition

Clinical implications of malnutrition

In **Chapter 6**, we explored the role of malnutrition at diagnosis and at 3, 6, and 12 months with respect to survival rates and risk of infection. We found that survival rates were worse in children undernourished according to BMI <-1.5 SDS at diagnosis and BMI <-1 SDS at 3 months. Weight loss in the first 3 months after diagnosis was associated with more bacterial infections during the first year. Weight loss, overnutrition at diagnosis and 3 months, and nutritional status at 6 and 12 months did not influence survival rates.
The added value of this study is that for the first time the consequences of weight loss have been demonstrated. Rapid weight loss appears to make children more vulnerable to bacterial infections. Similar to severe undernutrition, moderate undernutrition at diagnosis and at 3 months was also associated with reduced survival rates. This implies that nutritional support is required from the beginning of treatment to prevent weight loss and to improve nutritional status in children with BMI z-scores below -1 SDS.

The impact of malnutrition on health-related quality of life

Besides clinical implications, we also studied the impact of nutritional status on health-related quality of life (HRQOL). HRQOL was assessed by two different measures. Because HRQOL was measured longitudinally, first we tested whether these measures were sensitive to response shift. The response shift phenomenon was explored on two sequential measurements of HRQOL (**Chapter 7**). We found that both child- and parent-report ratings of overall HRQOL, measured using Cantril's ladder, were affected by response shift resulting in an underestimation of the change in HRQOL. In contrast, measurements of the PedsQL instruments were not biased by response shift. Therefore, the PedsQL measures are recommended in studies that assess changes in HRQOL over time.
The results of the Pecannut study indicate that both undernourished and overnourished children experienced worse HRQOL compared with well-nourished children (**Chapter 8**). Significant weight loss and weight gain also contributed to worse HRQOL. Previous studies have shown that children treated for cancer had significantly poorer HRQOL when compared with healthy children or children with other diseases.[17-20] The current study, however, demonstrates that under- and overnourished patients have the poorest HRQOL of all cancer patients. When examining the domains of HRQOL, undernourished children and children with weight loss reported impaired physical and social

functioning. In addition, undernourished children reported more side-effects of treatment. Overnourished children and children with weight gain reported worse functioning in the psycho-social domain, particularly in emotional and cognitive functioning. In contrast, parent-report scores of overnourished children were lower on social functioning.
These findings again stress the importance of a good nutritional status and of adequate nutritional support during treatment.

IMPLICATIONS FOR CLINICAL PRACTICE

The results of this thesis highlight important issues regarding the nutritional status in children with cancer. The main areas of concern are:

- underestimation of deterioration of the nutritional status at the time of diagnosis;
- significant weight loss in some children in the beginning of treatment;
- gain in weight and FM during treatment in all patient groups;
- relatively low FFM in all patient groups, particularly in children with brain malignancies;
- more bacterial infections and lower survival rates in undernourished children and children with significant weight loss;
- worse HRQOL in malnourished children and children with significant weight loss or weight gain.

These issues stress the importance of adequate nutritional support. Nutritional support aims to prevent or reduce nutritional deficits, to improve physical condition, to maintain growth and development, and to maximize HRQOL.[21] In order to achieve these goals, health care professionals (nurses, dietitians, and physicians) work together proactively with children and parents, each discipline offering its own knowledge and expertise. Nurses play a pivotal role in the assessment and monitoring of the nutritional status, as they aim to ensure an adequate dietary intake in children. Nurses are the first to notice (risk factors of) malnutrition and they can intervene immediately. In some cases, nurses may prevent or treat malnutrition independently; however, in more complicated cases, the specific expertise of the dietitian or physician is needed. Dietitians are the experts regarding nutrition and nutrients. Their expertise is essential to provide adequate nutritional support to this particular

patient group. Physicians are responsible for the treatment regimen and they aim to keep patients in a good nutritional condition so that they can finish their therapy. A good collaboration between nurses, dietitians, and physicians is therefore necessary for providing adequate nutritional support.
The first step in nutritional support consists of a nutritional assessment at the time of the first admission in order to identify those children with preexisting malnutrition or children at risk of malnutrition. Subsequently, nutritional status needs to be monitored and reassessed during therapy. Important elements of the nutritional assessment are anthropometry and estimations of energy requirements.[22] In the following paragraph, we will make recommendations for anthropometry and estimations of energy requirements. Lastly, the clinical implications of tube feeding and physical activity will be discussed.

Anthropometry

Body size

Accurate measurement of weight and height is essential to identify malnutrition. The measurements of weight and height must be plotted into growth curves to determine the child's nutritional status and to be able **to monitor longitudinal changes in nutritional status over the course of therapy** (Chapter 4).
In order to determine weight loss in the pre-admission period, **comparison of data of weight and height at diagnosis with data of growth curves from preventive health care centers is recommended** (Chapter 3) (see Box1 for further details).

Body composition

Given the deviations in body composition and the serious consequences of low FFM and high FM in children with cancer, **assessment and monitoring of body composition is recommended** (Chapters 4 and 8). Skinfold measurement may be used to assess muscle and fat stores (see Box 2 for further details). The triceps skinfold measure in particular has been found to correlate well with fat mass.[23,24] Skinfold measurements are simple and quick to obtain in most age groups; however, in obese children precision and accuracy is poor.[25] Unfortunately, skinfold reference data are not always available or, in the case of the Netherlands, are very outdated.
Mid-upper arm circumference (MUAC) is very simple and quick to measure. Also, contrary to weight, MUAC is not sensitive to fluid alterations in the body. Although MUAC is referred to as a measure for muscle mass,[26,27] it actually

measures muscle, bone, and fat mass of the upper-arm. In the Pecannut study, MUAC had higher correlations with BMI (r= 0.8) and FM (r= 0.5-0.7) than with FFM (r= 0.4-0.5). Therefore, **MUAC is recommended as a surrogate measure for BMI** in patients with edema or in patients in whom measurements of weight and height are nor possible.
Bio-electrical impedance (BIA) measures impedance by sending a small electrical current through the body. Total body water (TBW) and FFM are estimated using special equations adjusted for age, gender, weight and height.[25,28] Although BIA is quick, simple, and acceptable to children, it is insufficiently accurate in its estimations of body composition in individuals. In addition, population specific equations are required to estimate FFM. Unfortunately, such equations are not available yet for children with cancer.

Energy requirements

Contrary to the general opinion, **we found that energy requirements in children treated for cancer were lower than in healthy children and lower than RDA** (Chapter 5). In fact, RDA is not an appropriate norm for energy requirements during cancer treatment. Energy requirements are best estimated using the following equation:

Energy requirement = (RMR x PAL x GF)/EAC[4]

This prediction formula is recommended by the Dutch Malnutrition Steering Group[4] and includes metabolic rate (RMR), calculated using Schofield's equations;[5] physical activity (PAL); growth (GF); and energy absorption coefficient (EAC). We have omitted the illness factor from the equation because the evidence for increased energy requirements due to an increased metabolic rate is inconclusive[29] and because our results (without using the illness factor) matched with changes in nutritional status. The equation provides a global estimation of the child's energy requirements and is a starting point for the dietary advice given to the child. However, given that all factors in the equation rely on rough estimations and given that some factors can fluctuate, for instance, the level of physical activity, **close monitoring of weight is necessary to evaluate the adequacy of the energy intake.**

Tube feeding

In the Netherlands, tube feeding is the method of choice for children with insufficient oral intake who require intervention. **When calculating the**

amount of required nutrition for tube fed patients, it is important to control for the low level of activity in these patients. In general, children who require tube feeding experience more side effects of treatment, feel sicker, and are less active. These factors lower their energy requirements. During the period of tube feeding, **close monitoring of weight and fat mass is recommended in order to prevent overfeeding**. In addition, children should be encouraged to be as active as their physical condition allows.

Physical activity

The level of physical activity was found to be the main factor contributing to increase in fat mass during treatment (Chapter 4). **Children with cancer should be stimulated to be as active as possible** within the limitations set by their illness or therapy. Improving the level of physical activity will be a great challenge because children often feel very sick during therapy. To date, several intervention programs have been developed that provide special training sessions to improve the level of activity.[30] A disadvantage of these training sessions is that these are an additional burden to all the other obligations (hospital visits, school, care of siblings) children and parent experience, and the sessions only cover a defined period of time. After completing the training program, many children will relapse into their previous behavior patterns. Therefore, to improve children's level of physical activity, we believe physical activity should be incorporated into their daily routine. In addition to receiving advice about the relevance of an adequate dietary intake, the relevance of physical activity from the start of treatment should also be stressed to children and parents. Raising awareness is the first step towards a more active lifestyle. Second, children and parents need to be advised about performing daily activities in an active way, for example, brushing one's teeth while standing in front of the washbowl instead of lying in bed. In addition, more emphasis should be placed on active leisure time. Play and enjoyment are integral to an active life style.

At this moment, the Department of Pediatric Oncology and Hematology of the University Medical Center Groningen in collaboration with The Knowledge Center for Technology and Innovation of the University of Applied Sciences in Utrecht, has started a project to develop "tools" to improve dietary intake and physical activity in pediatric cancer patients. The project POKO (Participatief Ontwerpen voor de Kinderoncologie) aims to find solutions that will help children to become more active by means of close and interactive cooperation between children, parents, and professionals. Testing of the first prototypes of the tools developed in this project is expected for autumn 2014.

FUTURE RESEARCH

The Pecannut study has generated valuable insights into the patterns of weight and body composition in children treated for cancer. Moreover, our study has provided further evidence for the importance of a good nutritional status in this particular patient group. The findings of our study have important implications for clinical practice and offer relevant information for future studies. Five areas of future research are discussed below.

Assessment of body composition

In order to measure body composition in clinical practice using BIA, the development of specific equations for children with cancer or validation of existing equations against deuterium dilution, or dual-energy X-ray absorptiometry (Dexa) is recommended. BIA relies on the assumption that FFM is constant. However, hydration and density of FFM vary during maturation[31] and may vary during the disease period as well. The equation of Goran,[32] used in the Pecannut study, was found to be the best model for predicting TBW and FFM in healthy children and children with AIDS.[33] However, whether this equation is valid for children with cancer has never been tested.

Another promising method to assess body composition in clinical practice is the air-displacement plethysmography (ADP). ADP is similar to hydrodensitometry, yet ADP uses air displacement within a closed system as alternative for water. ADP, performed by Bod Pod, is non-invasive and acceptable to children.[25,34] However, ADP has the same pitfalls as BIA, in that population specific equations are needed for adequate estimation of FM and FFM in children treated for cancer. [25,35]

Next to muscle mass (FFM), muscle function is a valuable indicator of both nutritional and functional status. Muscle function has been found to correlate with whole body protein,[36] and body cell mass.[37] In adult patients, measurement of hand grip strength as a measure of nutritional status has gained considerable attention.[38] Reduced hand grip strength has been found to be an important predictor for health outcomes such as length of hospital stay, functional status, and survival rates.[38] To our knowledge, in children hand grip strength has only been applied as a measure to evaluate muscle functions in relation to motor performance.[39,40] However, because hand grip strength is quick, easy, acceptable to children, insensitive to fluid imbalances, and does not require skilled professionals, it is worth studying the applicability of this method to assess muscle function and muscle mass in children treated for cancer.

Estimation of energy requirements

Because it is not certain whether metabolic rate is increased at diagnosis or during treatment, indirect calorimetry should be measured longitudinally in large samples and in different diagnostic categories (not only in patients with ALL). In addition, more research is needed on inflammatory processes and on the impact of inflammation on nutritional status. To date, inflammation in relation to cachexia has hardly been studied in childhood cancer. Such studies might contribute to better estimations of energy requirements and nutritional interventions that are better tailored to the patients' needs.

Method of feeding

In the Netherlands, nasogastric tube feeding is the method of choice for improving nutrient intake even in children who require tube feeding for more than 3 months. PEG tubes (percutaneous endoscopic gastrostomy) are only placed in special situations, i.e., in children with a nasopharynx carcinoma. In other countries, however, placement of PEG tubes is part of routine care; a PEG is placed simultaneously with the Port-a-Cath (or Venous Access Port VAP) just before the start of chemotherapy. Proponents of tube feeding claim that tube feeding is less invasive than PEG feeding and that PEG feeding is associated with many potential complications such as wound infection, necrotizing fasciitis, and peristonal leakage.[41] In contrast, proponents of PEG feeding argue that tube feeding places a great burden on children and that it is less acceptable to children and parents than PEG feeding. To date, no consensus has been reached on which intervention should be used. Therefore, future studies are needed that evaluate patient preferences, efficacy of feeding, and complications of both methods.
In addition, systematic research is recommended to compare the benefits and drawbacks of enteral feeding versus parenteral feeding. It is believed that enteral feeding should be preferred above parenteral feeding in order to keep the gastro-intestinal tract functioning. However, evidence for this assumption is lacking.

Improvement of physical activity

The alterations in body composition as demonstrated in our study are of serious concern. Therefore, intervention studies that aim to improve children's body composition are urgently needed. As was stated in the section on clinical implications, measures should be developed to increase the level of physical activity. Subsequently, intervention studies are needed to examine the efficacy of such measures.

Evidence based guidelines

Guidelines for nutritional support should be more evidence-based. Additional research is recommended, among others, to define the best criteria for a nutritional risk assessment. Existing pediatric screening tools, for instance, STRONG-kids,[42] differentiate insufficiently in the childhood cancer population. Currently, a special assessment tool for children with cancer called Pediatric Oncology Nutritional Screening Tool (PONS) is under development and awaiting validation in clinical practice.

Finally, as one of the ambitions of the coming decades is to improve quality of life of children treated for cancer (Chapter 1), HRQOL should be included as an outcome measure in future studies that aim to improve feeding practices, nutritional status, and physical activity.

GUIDELINES FOR CLINICAL PRACTICE BASED ON THE PECANNUT STUDY

Box 1. Body size: measurement of weight and height

- Measure weight and height at diagnosis and regularly during treatment (height monthly and weight at least weekly).
- Determine the child's nutritional status prior to the cancer diagnosis by asking parents and child for recent measurements of weight and height or by using data from the so-called "Groene boekje" from the preventive health care center (PHCC) (Chapter 3).
- Plot measurements of weight and height in growth charts and monitor changes in nutritional status over the course of therapy (Chapter 4).
- For infants (aged <1 year) growth curves of weight-for-age (WFA) are used; whereas for children 1 year and older weight-for-height (WFH) (or BMI-for- age) are used to define the nutritional status.[43]
- Set a target value for WFA and WFH. For some children this target value can be -1 SDS; whereas for other children a target value of +2 SDS is acceptable. This depends on the child's stature and nutritional status before the cancer diagnosis.
- Cut-off scores of <-2 SDS define undernutrition; whereas scores of >2 SDS define overnutrition.
- Report deviations of >0.5 SDS because an increase or decrease of >0.5 SDS may have impact on the child's condition (Chapter 8). A gradual change in weight may indicate an increase or decrease in body mass; however, rapid weight changes frequently indicate fluid retention or depletion.
- Growth curves can be plotted on paper or in digitalized programs, for instance, Growth Analyzer. An advantage of a digitalized system is that SDS scores are calculated and changes can be identified immediately. In addition, a digitalized system is accessible to more professionals working from different places.
- MUAC is recommended as a surrogate measure for BMI in patients with edema or in patients in whom measurements of weight and height are nor possible.

Box 2. Body composition: measurement of fat mass and fat free mass

- To determine fat mass, skinfold measurement is recommended, in particular triceps skinfold.
- Skinfold measurement should only be taken by specially trained professionals (nurses, dietitians, physicians).
- Skinfold data are best used as raw data or should be converted to standard deviation scores and growth curves.
- In obese children, precision and accuracy of skinfold measurement is poor because of the large skinfolds.
- MUAC is not an accurate measure for fat free mass. It corresponds better with BMI than with fat mass.
- As long as specific equations to estimate total body water and fat free mass in children with cancer are not available, bio-electrical impedance is insufficiently accurate in its estimation of body composition in individual patients.

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APPENDICES

- Nederlandse samenvatting
- List of publications
- List of conferences
- Dankwoord
- Curriculum Vitae
- Research Institute SHARE: previous dissertations

NEDERLANDSE SAMENVATTING

INTRODUCTIE

Florence Nightingale, één van de grondleggers van de verpleegkunde, toonde als eerste de meerwaarde aan van het systematisch verzamelen en analyseren van gegevens. Tijdens de Krim oorlog (1853-1856) liet zij door middel van zelf verzamelde gegevens en grafieken zien dat de sterfte in de militaire ziekenhuizen grotendeels werd veroorzaakt door besmettelijke ziekten als cholera en typhus. Nadat zij hygiënische maatregelen had ingevoerd nam de sterfte aanzienlijk af. In feite was Florence Nightingale de eerste die de relevantie van verpleegkundig onderzoek aantoonde. Haar benadering waarbij eenvoudige gegevens zoals gewicht, temperatuur en klachten worden verzameld is erg waardevol en kan een belangrijke bijdrage leveren aan het verbeteren van de zorg.
Bij kinderen met kanker levert het eten vrijwel altijd problemen op: veel kinderen eten weinig omdat het eten niet smaakt of omdat ze zich te ziek voelen. Andere kinderen hebben juist veel trek door de dexamethason en willen het liefst de hele dag eten. Sommige kinderen vallen heel erg af en raken ondervoed terwijl andere kinderen juist dikker worden. De problematiek is duidelijk divers. In de Pecannut studie is getracht door middel van het registreren van ondermeer gewicht en voedingsintake deze problematiek in kaart te brengen. Er is gekeken naar het verloop van de voedingstoestand, de factoren die van invloed zijn op gewichtsverlies of gewichtstoename en naar de consequenties van een slechte voedingstoestand.
In de volgende paragrafen worden achtereenvolgens de belangrijkste resultaten en de klinische relevantie van de Pecannut studie besproken en suggesties gedaan voor vervolgonderzoek.

RESULTATEN: WAT IS BEKEND

Hoewel er al meer dan veertig jaar onderzoek wordt gedaan naar de voedingstoestand van kinderen met kanker, is nog steeds niet duidelijk hoe groot het probleem van ondervoeding is **(Hoofdstuk 2)**. De meeste studies op het gebied van de voedingstoestand betreft kinderen met leukemie of betreft enkel de voedingstoestand bij diagnose of er zijn gegevens van slechts een kleine groep kinderen. Daarnaast wordt ondervoeding steeds verschillend gedefinieerd waardoor resultaten niet onderling vergeleken kunnen worden.

Verder is niet bekend in welke fase van de behandeling kinderen afvallen of juist zwaarder worden. Over het algemeen wordt aangenomen dat kinderen afvallen omdat ze te weinig eten of omdat hun stofwisseling verhoogd is door de kanker. Uit de literatuur studie (Hoofdstuk 2) blijkt echter dat het bewijs voor verhoogde stofwisseling niet overtuigend is. Verder blijkt dat kinderen met kanker weliswaar minder eten dan wordt aanbevolen, maar dat niet onderzocht is of ze door minder te eten ook afvallen. Bovendien zijn de kinderen door hun ziekte weinig actief waardoor het lichaam met minder energie kan volstaan.
Tenslotte is er nog weinig onderzoek gedaan naar inflammatie, een ontstekingsproces in het lichaam dat kan leiden tot gewichtsverlies en cachexie (= ernstige vorm van ondervoeding met verlies van spiermassa veelal veroorzaakt door ziekte). Er zijn bij diagnose in het bloed van kinderen stoffen aangetroffen die duiden op een onstekingsproces. Maar een verband tussen inflammatie en gewichtsverlies is bij kinderen met kanker nog niet aangetoond. Naar aanleiding van deze bevindingen is vervolg onderzoek nodig dat zich richt op:

- Het in kaart brengen van de voedingstoestand gedurende het traject van de behandeling van kinderen met verschillende types kanker.
- Het vaststellen van de energiebehoeftes en het vaststellen van de gevolgen van energietekort op de voedingstoestand.
- Het meten van inflammatie en de gevolgen van inflammatie op de voedingstoestand.
- De eerste twee punten zijn in de Pecannut studie onderzocht.

RESULTATEN: WAT IS NIEUW

Prevalentie van ondervoeding

Bij diagnose was 2% van de kinderen ondervoed volgens gewicht-naar-leeftijd <-2 standaard deviatie score (SDS), 4% volgens lengte-naar-leeftijd <-2 SDS en 7% volgens gewicht-naar-lengte <-2 SDS. (**Hoofdstuk 3**). Echter, wanneer gewicht en lengte van een kind bij diagnose vergeleken werden met de gegevens van de eigen groeicurves (afkomstig van het Groene boekje van het consultatiebureau), dan hadden meer kinderen een slechte voedingstoestand. Bij 20-24% van de kinderen waren de z-scores voor gewicht-naar-leeftijd, lengte-naar-leeftijd, of gewicht-naar-lengte meer dan 0.5 SDS lager. In feite

waren deze kinderen ook ondervoed en is hun voedingstoestand slechter dan de metingen bij diagnose lieten zien. Dit betekent dat indien er alleen naar gewicht en lengte bij diagnose gekeken wordt een deel van de kinderen met een slechte voedingstoestand over het hoofd wordt gezien.
Gedurende de 12 maanden na diagnose namen gewicht, body mass index (BMI) en percentage vetmassa toe (**Hoofdstuk 4**). Bij kinderen met een hersentumor nam het gewicht meteen na diagnose toe, terwijl de BMI van kinderen met een hematologische maligniteit of een solide tumor eerst daalde om vervolgens ook te stijgen. Het aantal kinderen met overvoeding (BMI >2 SDS) verdubbelde van 5% bij diagnose tot 10% na 12 maanden. Tegelijkertijd nam het aantal ondervoede (BMI <-2 SDS) kinderen af van 8% bij diagnose tot 2% na 12 maanden. Indien ook de hoeveelheid vetmassa en vetvrije massa meegenomen werd als criterium voor de voedingstoestand dan was het aantal kinderen met onder- of overvoeding groter (zie hoofdstuk 4). In tegenstelling tot de hoge vetmassa was de vetvrije massa (= maat voor spiermassa) bij diagnose al laag en bleef laag gedurende de behandeling; ongeveer 17% van de patiënten was ondervoed op basis van een lage vetvrije massa. Van alle patiënten hadden de kinderen met een hersentumor de laagste vetvrije massa en de hoogste vetmassa. De toename in vetmassa was gelijk voor kinderen met hematologische maligniteiten, solide tumoren en hersentumoren.
Naast een lage BMI of lage vetvrije massa, had 28% van de patiënten ernstig (>0.5 SDS) gewichtsverlies in de eerste 3 maanden na diagnose. Gewichtsverlies kwam met name voor bij kinderen met hematologische maligniteiten en solide tumoren. Uit de resultaten in hoofdstuk 6 bleek, dat juist deze groep kinderen een grotere kans had op infecties.
Al met al blijkt dat de voedingstoestand bij kinderen met kanker complex is. Kinderen met kanker hebben niet alleen te maken met ondervoeding, gewichtsverlies en een lage vetvrije massa, maar ze worden ook geconfronteerd met overvoeding en een hoge vetmassa. Deze veranderingen in voedingstoestand zijn zorgelijk zowel voor de korte als voor de lange termijn; want uit de literatuur blijkt dat survivors van kinderkanker zelfs jaren na het beëindigen van de behandeling een hoge vetmassa en hoge BMI hebben. De huidige studie laat zien dat in geïndustrialiseerde landen de focus wellicht teveel ligt op de behandeling van ondervoeding waardoor overvoeding wordt gemist.

Verklarende factoren van een slechte voedingstoestand

Voedingsintake

De voedingsintake is één van de belangrijkste factoren voor de voedingstoestand. Een te lage intake leidt tot gewichtsverlies, terwijl een te hoge intake leidt tot gewichtstoename. In **Hoofdstuk 5** wordt beschreven hoe deze samenhang is bij kinderen met kanker. De energie intake van de kinderen was gemiddeld 105% van hun energiebehoefte volgens de berekening met de Schofield vergelijking (= een formule om per kind de energiebehoefte te berekenen). Echter, de intake was 80% van de algemene dagelijkse hoeveelheid (ADH) van het Voedingscentrum en 84% van de intake van gezonde kinderen. Dus de intake van kinderen met kanker kwam in grote lijnen overeen met hun berekende energiebehoefte, maar was vergeleken met de andere normen te laag. Echter de toename in gewicht, BMI en vetmassa zoals beschreven in hoofdstuk 4, suggereert dat de energie intake in ieder geval voldoende of zelfs iets te hoog was. Dit betekent dat kinderen met kanker kennelijk een lagere energiebehoefte hebben dan de normen volgens de ADH en ook een lagere energiebehoefte hebben dan gezonde kinderen.

De energie intake was negatief gecorreleerd met de voedingstoestand; naar verhouding was de intake van dunne en lichte kinderen hoger dan de intake van zware en dikke kinderen. Een voor de hand liggende verklaring is dat dunne en lichte kinderen vaker sondevoeding hadden en daardoor een hogere intake. Een andere mogelijke verklaring is het feit dat de intake gemeten werd tussen de chemokuren en niet tijdens de chemokuren. Mogelijk is de hoge intake van de dunne kinderen tussen de kuren een compensatie van hun lage intake tijdens de kuren.

Een ander resultaat beschreven in hoofdstuk 5 is dat de eiwit intake bijna twee maal zo hoog was als de ADH en als de individuele behoefte. Echter, de hoge eiwit intake bleek geen gunstig effect te hebben op de vetvrije massa. Zoals beschreven in hoofdstuk 4 was de vetvrije massa onveranderd laag vanaf het begin van de behandeling. Het is mogelijk dat de benodigde eiwitintake om de vetvrije massa te verhogen hoger is dan de huidige normen. Daarnaast is een bepaald niveau van lichamelijke activiteit noodzakelijk om de vetvrije massa te verbeteren terwijl kinderen met kanker juist minder actief zijn vanwege hun ziekte en intensieve behandeling.

Patiënten kenmerken, behandelingsfactoren en lichamelijke activiteit

Naast energie intake is gekeken naar de samenhang tussen veranderingen in voedingstoestand en patiënten kenmerken, behandelingsfactoren en lichamelijke

activiteit (**Hoofdstuk 4**). Het type kanker was de enige factor van invloed op het gewichtsverlies in het begin van de behandeling; kinderen met hematologische maligniteiten en solide tumoren vielen in het begin af, terwijl het gewicht van kinderen met hersentumoren vanaf het begin al toenam. De toename van de BMI in de eerste 3 maanden na diagnose hing samen met een slechte voedingstoestand bij diagnose en het toedienen van sondevoeding. De snelle toename van BMI van kinderen met een slechte voedingstoestand bij diagnose kan beschouwd worden als inhaalgroei. Zoals beschreven in Hoofdstuk 3 waren lengte en gewicht bij diagnose lager dan was geschat op basis van de groeicurves. Inhaalgroei is welbeschouwd een wenselijke vorm van gewichtstoename. Daarnaast nam de BMI van kinderen met sondevoeding meer toe dan van kinderen die zelf aten. Over het algemeen beoogt sondevoeding de voedingstoestand te verbeteren. Echter, het is lastig om de grens te bepalen tussen inhaalgroei en overvoeden. Aangezien gedurende de 12 maanden na diagnose het gewicht bleef stijgen en de z-scores van gewicht tijdens behandeling (Hoofdstuk 4) hoger waren dan de z-scores gebaseerd op de groeicurves (Hoofdstuk 3), is onze conclusie dat de toename van het gewicht zowel te verklaren is door inhaalgroei als door overvoeden als gevolg van sondevoeding. De resultaten beschreven in Hoofdstuk 5 bevestigen dat de gemiddelde energie intake hoger was dan de behoefte van de patiënten en dat de intake bij kinderen met sondevoeding 10% hoger was dan bij kinderen die zelf eten. In een poging om ondervoeding te voorkomen of te behandelen, werden kinderen te agressief gevoed met overgewicht tot gevolg.

In tegenstelling tot andere studies hebben wij geen verband gevonden tussen de toename van BMI en leeftijd, geslacht of BMI van de ouders, noch hebben we een verband gevonden tussen toename van BMI en intensiteit van de behandeling, klachten of lichamelijk activiteit. Deze laatste drie factoren hingen samen met sondevoeding, waardoor sondevoeding de belangrijkste verklarende factor voor gewichttoename is. Het gebruik van corticosteroïden wordt vaak in verband gebracht met de toename in BMI, omdat kinderen meer eten ten tijde van de behandeling met corticosteroïden. Echter, studies naar de relatie tussen corticosteroïden en BMI laten tegenstrijdige resultaten zien. In onze studie hebben we geen verband gevonden tussen toename van BMI en gebruik van corticosteroïden.

Een laag niveau van fysieke activiteit bleek bij te dragen aan de stijging van het percentage vetmassa. Dit komt overeen met bevindingen bij gezonde kinderen en adolescenten. Net als bij de stijging van de BMI was de verwachting dat een hoge energie intake of behandeling met corticosteroïden de oorzaak zou

zijn van de stijging in vetmassa. Maar net als bij de BMI werd een dergelijke relatie niet gevonden. Fysieke activiteit was de enige verklarende variabele voor de stijging in percentage vetmassa. Kinderen met kanker zijn weinig actief, maar hun energie intake is voldoende of zelfs meer dan voldoende. Door deze positieve energie balans nam hun gewicht toe en deze toename was in de vorm van vetmassa.
Samengevat, energie intake wordt geacht de belangrijkste verklarende factor voor de voedingstoestand te zijn. Maar uit de resultaten van de Pecannut studie blijkt dat in de klinische praktijk de samenhang tussen intake en voedingstoestand complex is. Niet de energie intake maar het toedienen van sondevoeding aan de groep kinderen die het meest ziek was, het minst actief en door de sondevoeding de hoogste intake had, was van invloed op de toename van de BMI. De positieve energie balans en een laag niveau van fysieke activiteit resulteerde in de toename van vetmassa. In feite spelen dezelfde mechanismen die bij gezonde kinderen obesitas veroorzaken ook een belangrijke rol bij het ontstaan van overvoeding bij kinderen met kanker.

Gevolgen van een slechte voedingstoestand

Klinische gevolgen van een slechte voedingstoestand

In **Hoofdstuk 6** is de relatie tussen een slechte voedingstoestand bij diagnose, 3, 6 en 12 maanden en overleving en risico op infecties bestudeerd. Ondervoede kinderen met een BMI <-1.5 SDS bij diagnose en een BMI <-1 SDS 3 maanden na diagnose hadden slechtere overlevingskansen. Kinderen met gewichtsverlies in de eerste 3 maanden hadden meer bacteriële infecties in het eerste jaar na diagnose. Gewichtsverlies, overvoeding bij diagnose en 3 maanden en de voedingstoestand bij 6 en 12 maanden hadden geen invloed op de overlevingskansen.
De meerwaarde van deze studie is dat voor de eerste keer de negatieve gevolgen van gewichtsverlies zijn aangetoond. Gewichtsverlies lijkt de kinderen vatbaarder te maken voor bacteriële infecties. Verder blijkt dat net als ernstige ondervoeding ook matige ondervoeding bij diagnose en 3 maanden na diagnose gerelateerd te zijn aan lagere overlevingskansen. Dit betekent dat vanaf de start van de therapie voedingszorg noodzakelijk is om gewichtsverlies te voorkomen en de voedingstoestand van kinderen met een lage BMI te verbeteren.

De impact van een slechte voedingstoestand op kwaliteit van leven

Naast de klinische gevolgen van een slechte voedingstoestand hebben we ook gekeken naar de impact van een slechte voedingstoestand op de gezondheidsgerelateerde kwaliteit van leven. Kwaliteit van leven werd gemeten met twee verschillende instrumenten. Aangezien we herhaalde metingen deden van kwaliteit van leven hebben we eerst gekeken of deze instrumenten gevoelig ware voor response shift (= herbeoordeling door verandering in gezondheid). Het effect van response shift werd op twee opeenvolgende metingen van kwaliteit van leven bestudeerd (**Hoofdstuk 7**). Uit deze studie bleek dat zowel de scores van kinderen als van ouders van de overall kwaliteit van leven, gemeten met Cantril's ladder, beïnvloed werden door response shift. Dit resulteerde in onderschatting van de verbetering in kwaliteit van leven. Daarentegen werden de metingen van de PedsQL instrumenten niet beïnvloed door response shift. Daarom kunnen studies die veranderingen van kwaliteit van leven willen meten het beste de PedsQL instrumenten gebruiken. Uit de Pecannut studie bleek verder dat zowel ondervoede als overvoede kinderen een slechtere kwaliteit van leven hadden dan goed gevoede kinderen met kanker (**Hoofdstuk 8**). Een gewichtsverlies of toename >5% leidde ook tot een slechtere kwaliteit van leven. Eerder onderzoek toonde aan dat vergeleken met gezonde kinderen of kinderen met andere aandoeningen kinderen met kanker de slechtste kwaliteit van leven hadden. Uit de huidige studie bleek dat ondervoede en overvoede kinderen met kanker de aller-slechtste kwaliteit van leven hadden van alle kanker patientjes. Betreffende de verschillende domeinen van kwaliteit van leven presteerden ondervoede kinderen en kinderen met gewichtsverlies slechter in fysiek en sociaal functioneren. Daarnaast hadden ondervoede kinderen meer last van bijwerkingen van de behandeling. Overvoede kinderen en kinderen met toename van gewicht presteerden slechter op het psychosociale vlak, in het bijzonder in emotioneel en cognitief functioneren.

Deze resultaten laten opnieuw zien dat tijdens de kankerbehandeling een goede voedingstoestand en adequate voedingszorg uiterst belangrijk zijn.

KLINISCHE RELEVANTIE

Dit proefschrift stipt een aantal belangrijke punten aan met betrekking tot de voedingstoestand van kinderen met kanker. De belangrijkste punten zijn:

- de verslechtering van de voedingstoestand bij diagnose wordt onderschat;
- een deel van de kinderen heeft in het begin van de behandeling ernstig gewichtsverlies;
- uiteindelijk nemen het gewicht en de vetmassa toe zowel bij kinderen met hematologische maligniteiten als bij kinderen met solide en hersentumoren;
- kinderen met kanker hebben een relatief lage vetvrije massa, in het bijzonder de kinderen met een hersentumor;
- ondervoede kinderen en kinderen met gewichtsverlies hebben respectievelijk een slechtere overlevingskans en meer bacteriële infecties;
- ondervoede, overvoede kinderen en kinderen met gewichtsverlies of toename hebben een slechtere kwaliteit van leven.

Uit al deze punten blijkt dat goede voedingszorg belangrijk is. Het doel van voedingszorg is het voorkomen of verminderen van voedingstekorten, het verbeteren van de fysieke conditie, het handhaven van groei en ontwikkeling en het optimaliseren van de kwaliteit van leven. Samen met kind en ouders werken de zorgprofessionals (verpleegkundigen, diëtistes, artsen) aan deze doelen, iedere discipline met zijn of haar eigen kennis en vaardigheden. Verpleegkundigen spelen een belangrijke rol in het vaststellen en monitoren van de voedingstoestand en zij dragen zorg voor een adequate voedingsintake. De verpleegkundige is veelal de eerste die (het risico op) ondervoeding signaleert en zij kan meteen ingrijpen. In sommige gevallen kan de verpleegkundige zelfstandig ondervoeding voorkomen of behandelen. Echter, in meer complexe gevallen is de specifieke kennis van de diëtiste of arts nodig. Diëtistes zijn de echte specialisten op het gebied van voeding en voedingsmiddelen. Hun kennis is essentieel om adequate voedingszorg te verlenen aan deze groep patiënten. Artsen zijn verantwoordelijk voor de behandeling en zij streven naar een goede fysieke conditie opdat de patiënten de behandeling goed aankunnen. Voor een optimale voedingszorg is een goede afstemming en samenwerking tussen deze drie professionals een vereiste.
Goede voedingszorg begint met het bepalen van de voedingstoestand om de kinderen met (risico op) ondervoeding te identificeren. Vervolgens wordt de voedingstoestand gedurende de behandeling gevolgd en geëvalueerd.

Belangrijke elementen om de voedingstoestand te bepalen zijn antropometrie (= het meten van mensen, bijvoorbeeld het meten van lengte en gewicht) en het berekenen van de energiebehoefte. In de volgende paragraaf zullen we hier een aantal aanbevelingen over geven. Tenslotte, zullen we de consequenties van sondevoeding en van geringe fysieke activiteit bespreken.

Antropometrie

Gewicht en lengte

Het bepalen van de voedingstoestand begint met meten van gewicht en lengte overeenkomstig de richtlijnen. Vervolgens **worden gewicht en lengte genoteerd in groei-curves** om een goede inschatting te maken van de voedingstoestand en **om veranderingen gedurende de behandeling te kunnen volgen** (Hoofdstuk 4).

Ten einde gewichtsverlies voorafgaande aan de diagnose te kunnen vaststellen is het advies om **gewicht en lengte bij diagnose te vergelijken met de eigen groeicurves van het kind** (Hoofdstuk 3) (zie Box 1 voor toelichting).

Lichaamssamenstelling

Gezien de afwijkende lichaamssamenstelling en de ernstige gevolgen van een lage vetvrije massa en een hoge vetmassa bij kinderen met kanker, wordt aanbevolen de **lichaamssamenstelling te meten en te monitoren**. Met behulp van huidplooimetingen kunnen vetmassa en vetreserves gemeten worden (zie Box 2 voor toelichting). Met name de triceps huidplooi is een goede maat voor vetmassa. Huidplooimetingen zijn relatief eenvoudig en snel te meten en geschikt voor de meeste leeftijdscategorieën. Echter, bij obese kinderen is de meting minder nauwkeurig. Helaas beschikken niet alle landen over referentie gegevens van de huidplooien, of ze zijn zoals in Nederland, niet erg recent.

De bovenarmomtrek is eenvoudig en snel te meten. In tegenstelling tot het gewicht is de bovenarmomtrek niet zo gevoelig voor schommelingen in de vochtbalans. Hoewel de bovenarmomtrek over het algemeen gezien wordt als een maat voor spiermassa, meet het eigenlijk spiermassa, bot en vetmassa. In de Pecannut studie bleek de bovenarmomtrek sterker geassocieerd met de BMI (r=0.8) en de vetmassa (r=0.5-0.7) dan met de vetvrije massa (r=0.4-0.5). **De bovenarmomtrek is dan ook een goed alternatief voor de BMI** bij kinderen met oedeem of bij kinderen bij wie metingen van gewicht en lengte niet mogelijk zijn.

Bio-electrische impedantie analyse (BIA) meet de impedantie door een lage stroom door het lichaam te sturen. Het totale lichaamswater en de

vetvrije massa worden geschat met behulp van speciale formules waarin leeftijd, geslacht, gewicht en lengte worden meegenomen. Vervolgens kan dan de vetmassa berekend worden. Hoewel de BIA snel, eenvoudig en acceptabel is voor kinderen, is de nauwkeurigheid van de schatting van de lichaamssamenstelling op patiëntniveau onvoldoende. Bovendien zijn voor een goede schatting speciale formules nodig voor kinderen met kanker en die zijn er helaas nog niet.

Energiebehoefte

In tegenstelling tot de algemene opvatting toonden we in de Pecannut studie aan dat **de energiebehoefte bij kinderen met kanker lager is dan bij gezonde kinderen en lager is dan de ADH** (Hoofdstuk 5). In feite is de ADH qua energiebehoefte geen goede norm voor deze kinderen. Voor het bepalen van de energiebehoefte is het beter de formule van de Stuurgroep Ondervoeding te hanteren:

Energiebehoefte = (RMR x AF x GF)/EAC

RMR staat voor rustmetabolisme berekend met de Schofield formule; AF betekent actviteitsfactor; GF is groeifactor; en EAC is energieabsorptiecoëfficiënt. Wij hebben de ziektefactor in de formule achterwege gelaten aangezien het bewijs voor verhoogde energiebehoefte als gevolg van een verhoogd metabolisme niet overtuigend is en omdat de resultaten van onze studie (zonder meenemen van de ziektefactor) overeenkwamen met de verandering in voedingstoestand. De formule geeft een globale schatting van de energiebehoefte van het kind en vormt de basis van het voedingsadvies. Echter, aangezien alle factoren in de formule gebaseerd zijn op globale schattingen en sommige van deze factoren kunnen veranderen, bijvoorbeeld het niveau van fysieke activiteit, **is het nauwlettend volgen van het gewicht noodzakelijk om de energie intake te kunnen evalueren.**

Sondevoeding

In Nederland is sondevoeding de eerste keus als orale voeding niet lukt. **Bij het berekenen van de benodigde hoeveelheid sondevoeding is het belangrijk rekening te houden met de verminderde activiteit van de kinderen.** Over het algemeen zijn de kinderen met sondevoeding zieker, ervaren ze meer bijwijkingen van de behandeling en zijn ze minder actief. Hierdoor is hun energiebehoefte lager. **Gedurende de periode dat de kinderen sondevoeding**

krijgen is het belangrijk om het gewicht en vetmassa nauwlettend te volgen om overvoeden te voorkomen. Daarnaast is het belangrijk kinderen aan te moedigen om zo actief mogelijk te zijn.

Lichamelijke activiteit

Een geringe mate van lichamelijke activiteit bleek de belangrijkste verklarende variabele te zijn voor de stijging van vetmassa tijdens de behandeling (Hoofdstuk 4). Daarom **is het belangrijk om, binnen de beperkingen door de ziekte en behandeling, beweging zoveel mogelijk te stimuleren**. Echter, het stimuleren van bewegen is een grote uitdaging omdat de kinderen zich tijdens de behandeling vaak te ziek voelen. Er zijn tot nu toe een aantal interventieprogramma's ontwikkeld met speciale oefenprogramma's om beweging te stimuleren. Een nadeel van deze trainingsprogramma's is echter dat deelname aan een training een extra belasting is naast alle andere verplichtingen (ziekenhuisbezoek, school, zorg voor broertjes en zusjes) die kinderen en ouders al hebben. Een ander nadeel is dat deze programma's slechts gedurende een bepaalde tijdsperiode plaatsvinden. Na afronding van het programma zullen veel kinderen terugvallen in hun oude patroon. Een andere en wellicht betere manier om bewegen te bevorderen is door het bewegen onderdeel te maken van de dagelijkse routine. Naast het advies aan kind en ouders over het belang van goede voedingsinname, moet vanaf het begin van de behandeling ook het belang van voldoende bewegen worden benadrukt. Bewustwording is een eerste stap naar een actievere levensstijl. Vervolgens moeten kinderen en ouders geadviseerd worden hoe ze meer beweging kunnen toepassen in het dagelijkse leven. Bijvoorbeeld door de tanden te poetsen bij de wastafel in plaats van in bed. Daarnaast is het belangrijk actieve vormen van vrijetijdsbesteding te kiezen waarbij plezier en spel voorop moeten staan.

De afdeling Kinderoncologie/Hematologie van het Universitair Medisch Centrum Groningen en het lectoraat Co-design van de Hogeschool Utrecht werken samen aan een project om instrumenten te ontwikkelen voor het bevorderen van adequaat eet- en beweeggedrag bij kinderen met kanker. Het project POKO (Participatief Ontwerpen voor de Kinderoncologie) beoogt om samen met kinderen, ouders en professionals oplossingen te vinden om kinderen goed en gezond te laten eten en meer te laten bewegen. Naar verwachting zullen de eerst prototypes in het najaar van 2014 getest worden.

VERVOLGONDERZOEK

De Pecannut studie heeft waardvolle inzichten opgeleverd over het verloop van de voedingstoestand bij kinderen met kanker. Daarnaast heeft onze studie nieuw bewijs opgeleverd over het belang van een goede voedingstoestand voor deze groep kinderen. Tenslotte geeft onze studie, naast een aantal belangrijke aanwijzingen voor de klinische praktijk, ideeën voor vervolgonderzoek. Mogelijke onderwerpen voor toekomstig onderzoek zijn:

- Het ontwikkelen van een betrouwbare methode voor het meten van de lichaamssamenstelling in de klinische setting. Om BIA in de patiëntenzorg te kunnen gebruiken moeten speciale omrekenformules voor kinderen met kanker ontwikkeld worden. Andere mogelijkheden om lichaamssamenstelling bij deze groep kinderen te meten zijn air-displacement plethysmography door middel van Bod Pod of het meten van de spierfunctie door middel van handknijpkracht meting. Ook voor deze methodes geldt dat eerst nader onderzoek nodig is alvorens toepassing in de dagelijkse praktijk mogelijk is.
- Longitudinaal meten van het rust metabolisme in een grote groep kinderen met verschillen kankerdiagnoses om een goede inschatting te kunnen maken van de werkelijke energiebehoefte.
- De voor-en nadelen van voeding via de neussonde of via de PEG sonde (= sonde via buikwand in maag). Het huidige beleid in Nederland is om kinderen zoveel mogelijk via de neussonde te voeden ook als voor langere tijd sondevoeding nodig is. Terwijl in andere landen het plaatsen van een PEG behoort tot de routine handelingen en gelijktijdig gebeurt met het plaatsen van de VAP (Venous Access Port = implanteerbaar toedieningssysteem voor infuus). Tot nu toe is niet bekend welke methode het meest effectief is, de minste complicaties geeft of het prettigst is voor het kind. Daarnaast is onderzoek naar de voor-en nadelen van sondevoeding versus parenterale (= via het infuus) voeding wenselijk. De vraag is of bij ernstige mucositis (= slijmvliesontsteking) enteraal voeden beter is, zodat het maag-darmkanaal blijft functioneren, of dat volledige parenterale voeding beter is.
- Interventiestudies waarin het effect van meer bewegen op de vetmassa en spiermassa wordt onderzocht.
- Het ontwikkelen van evidence based richtlijnen voor voedingszorg waarin het hele traject vanaf anamnese tot voedingsinterventie wordt beschreven.

Tot slot, aangezien één van de ambities van de kinderoncologie is om de kwaliteit van leven van kinderen met kanker te verbeteren (Hoofdstuk 1), dient kwaliteit van leven een belangrijke uitkomst maat te zijn in studies die zich richten op het verbeteren van de voedingstoestand en de fysieke activiteit van kinderen met kanker.

ADVIEZEN VOOR DE PRAKTIJK GEBASEERD OP DE PECANNUT STUDIE

Box 1. Het meten van gewicht en lengte

- Meet gewicht en lengte bij diagnose en vervolgens regelmatig tijdens behandeling (lengte maandelijks en gewicht minimaal 1x per week).
- Maak een inschatting van de voedingstoestand van het kind voor diagnose door kind en ouders hiernaar te vragen of door gegevens van het Groene Boekje (van het Consultatiebureau) te gebruiken (Hoofdstuk 3).
- Zet gegevens van gewicht en lengte in groeicurves en houdt gedurende de behandeling veranderingen in de voedingstoestand in de gaten (Hoofdstuk 4).
- Voor zuigelingen (<1 jaar) worden de groeicurves gewicht-naar-leeftijd gebruikt; voor kinderen ouder dan 1 jaar worden gewicht-naar-lengte of BMI-naar-leeftijd wordt gebruikt.
- Bepaal een streefwaarde voor gewicht-naar-leeftijd of gewicht-naar-lengte. Voor sommige kinderen kan deze waarde -1 SDS zijn terwijl voor andere kinderen een streefwaarde van +2 SDS acceptabel kan zijn. Dat hangt af van de bouw en de voedingstoestand van het kind voor diagnose.
- De afkapwaarde voor ondervoeding is <-2 SDS; voor overvoeding >+2 SDS.
- Rapporteer afwijkingen van >0.5 SDS want een stijging of daling van >0.5 SDS kan van invloed zijn op de conditie van het kind (Hoofdstuk 8). Een geleidelijke gewichtsverandering duidt veelal op een toename of afname van vet- of spiermassa. Echter snelle gewichtsveranderingen worden vaak veroorzaakt door veranderingen in de vochtbalans.
- Groeicurves kunnen op papier getekend worden of in een computerprogramma zoals Growth Analyzer. Een voordeel van een gedigitaliseerd programma is dat SDS scores berekend worden en dat verandering meteen

zichtbaar zijn. Een ander voordeel is dat een digitaal programma door meerdere professionals en vanaf verschillende plaatsen toegankelijk is.
- Bovenarmomtrek is een goed alternatief voor de BMI bij kinderen met oedeem of wanneer het meten van gewicht en lengte niet mogelijk is.

Box 2. Het meten van vetmassa en vetvrije massa

- Huidplooimeting en in het bijzonder de meting van de triceps huidplooi is een goede methode voor het bepalen van de vetmassa.
- Huidplooimeting moet alleen door geschoolde professionals (verpleegkundigen, diëtistes, artsen) uitgevoerd worden.
- De gegevens van de huidplooimeting kunnen het beste als ruwe gegevens gebruikt worden of omgezet worden naar z-scores en groeicurves.
- Bij obese kinderen zijn door de dikke plooien de metingen minder betrouwbaar.
- De bovenarmomtrek is geen goede maat voor de vetvrije massa. De bovenarmomtrek komt meer overeen met de BMI en de vetmassa.
- Zolang er geen speciale formules zijn voor kinderen met kanker is bioelectrische impedantie analyse (BIA) te onnauwkeurig om bij individuele kinderen lichaamswater en vetvrije massa te schatten.

LIST OF PUBLICATIONS

LIST OF CONFERENCES

LIST OF PUBLICATIONS

Articles included in this thesis

Brinksma A, Huizinga G, Sulkers E, Kamps W, Roodbol P, Tissing W. Malnutrition in childhood cancer patients: a review on its prevalence and possible causes. *Crit Rev Oncol Hematol* 2012; 83: 249-75.

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Brinksma A, Roodbol PF, Sulkers E, Kamps WA, de Bont ES, Boot AM, Burgerhof JG, Tamminga RY, Tissing WJ. Changes in nutritional status in childhood cancer patients: A prospective cohort study. *Accepted for publication by Clinical Nutrition.*

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Loeffen EAH, Brinksma A, Miedema KGE, de Bock GH, Tissing WJE. Clinical implications of malnutrition in childhood cancer patients - infections and mortality. *Accepted for publication by Supportive Care in Cancer.*

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van Rijn M, Jansma J, Brinksma A, Bakker HD, Boers GH, Carbasius-Weber E, Douwes AC, van den Herberg A, Ter Horst NM, de Klerk JB, de Koning TJ, van den Ploeg L, Rubio-Gozalbo ME, Sels JP, Sengers RC, de Valk HW, Termeulen H, Zweers H, van Spronsen FJ. A survey of natural protein intake in Dutch phenylketonuria patients: insight into estimation or measurement of dietary intake. *J Am Diet Assoc* 2008; 108: 1704-7.

LIST OF CONFERENCES

Results of the Pecannut study have been presented at the following (inter) national conferences:

International conferences

2010
MASCC (Multinational Association of Supportive Care in Cancer) Vancouver

2011
ECCO (European Cancer Organisation) Stockholm

2012
MASCC New York
SIOP (International Society of Paediatric Oncology) London

2013
MASCC Berlin
SIOP Hongkong
Nutricia International Advisory Board Meeting Paediatrics Budapest

2014
International Conference on Nutrition and Growth Barcelona
Seminar about relevance of nutritional support in children with cancer Moskou
MASCC Miami
International Paediatric Psychology Conference Amsterdam
International Congress of Behavioral Medicine Groningen
European Doctoral Conference in Nursing Science Maastricht
SIOP Toronto

National conferences

2010
V&VN Oncologiedagen voor verpleegkundigen

2011
Pediatrische Psychologie Congres Nijmegen
V&VN Oncologiedagen voor verpleegkundigen

2013
V&VN Oncologiedagen voor verpleegkundigen
SKION (Stichting Kinderoncologie Nederland/Dutch Childhood Oncology Group) Shared Care Conference Amsterdam

2014
Hogeschool Utrecht Co-design voor kinderen met kanker Utrecht
Hanzehogeschool Groningen Symposium Pt-Global Groningen

DANKWOORD

CV

DANKWOORD

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CURRICULUM VITAE

Aeltsje Brinksma was born November 27, 1963, in Barradeel, the Netherlands. She is the second in a family of five children and has one older brother and three younger sisters. After attending the Stedelijk Gymnasium in Leeuwarden and graduating for her VWO-β in 1982, she decided to study nursing at the Hanze University of Applied Sciences in Groningen. In 1986, she received her Bachelor of Nursing degree, cum laude. In 1990, she commenced a Masters in Health Science at the Universities of Maastricht/Groningen and graduated in Nursing Science in 1993.

From 1986 to1997, Aeltsje worked as a pediatric nurse at the Beatrix Children's Hospital of the University Medical Center Groningen (UMCG), gaining experience in the fields of oncology, liver transplantation, cardiology, gastroenterology, neonatology, and general pediatrics. She led the project 'Nursing diagnosis, outcomes and interventions' for the Beatrix Children's Hospital, and she developed, implemented, and evaluated nursing diagnoses, interventions, and outcomes for pediatric nursing.

After working as a nurse for a good ten years, Aeltsje turned her focus to research. From 1997 to 2007, she coordinated the nursing research program of the UMCG, wrote research proposals for grants, supervised master and bachelor students during their research projects, and organized and chaired research meetings of researchers in nursing. She taught Nursing Science at the University of Groningen; lectured on evidence-based practice, nursing diagnosis, and nursing outcomes; and supervised student tutor groups. During this period, she was a member of the committee 'Research in Medical Technology Assessment' of the UMCG and evaluated grant proposals. She was also a member of the steering committee 'Optimizing nutritional status in the UMCG' and leader of the project 'Nutritional Assessment', which aimed to develop, implement, and evaluate the nutritional screening program of the UMCG.

Aeltsje commenced her PhD at the University of Groningen in 2007, entitled 'Nutritional status in children with cancer'. She closely cooperates with The Knowledge Center Technology and Innovation of the University of Applied

Sciences in Utrecht so as to develop 'tools' to improve dietary intake and physical activity in pediatric cancer patients.

Aeltsje has published on the subject of nutrition in childhood cancer in renowned international journals. She is a member of the International Pediatric Oncology Nutrition Group (IPONG) and has presented the results of her research at many (inter) national conferences. For an overview see page 238. She is one of the translators/editors of the Dutch version of the Handbook of Nursing Diagnosis by Lynda Carpenito. This book is used in many Dutch nursing training programs.

Aeltsje is married to Oscar Couwenberg. They have three children, Sybren (1995), Jelle (1997), and Wytske (2000).

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