From the Department of Women´s and Children´s Health
Karolinska Institutet, Stockholm, Sweden

IMPACT OF BODY MASS INDEX ON OUTCOME, TOXICITY AND PHARMACOKINETICS IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Christina Egnell Gustafsson

Karolinska Institutet

Stockholm 2023

All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2023

ISBN 978-91-8017-098-7
Cover illustration by Christina Egnell Gustafsson, created with BioRender.com.

Impact of body mass index on outcome, treatment-related toxicity and pharmacokinetics in patients with acute lymphoblastic leukemia

Thesis for Doctoral Degree (Ph.D.)

By

Christina Egnell Gustafsson

The thesis will be defended in public at Ulf von Euler, J3:06 BioClinicum. Karolinska Universitetssjukhuset, Solnavägen 30, 171 64 Solna, on Friday 24th of November 2023 at 09:00 a.m.

Principal Supervisor:
Associate professor Susanna Ranta
Karolinska Institutet
Department of Women´s and Children´s Health
Division of Pediatric Oncology and Surgery

Co-supervisor(s):
Professor Arja Harila
Uppsala University
Department of Women´s and Children´s Health
Division of Pediatric Oncology and Surgery

Associate professor Mats Heyman
Karolinska Institutet
Department of Women´s and Children´s Health
Division of Pediatric Oncology and Surgery

Opponent:
Professor Marry van den Heuvel-Eibrink
University of Utrecht
Department of Child health and Strategic program cancer
Princess Maxima Center for Pediatric Oncology

Examination Board:
Associate professor Samppa Ryhänen
University of Helsinki
Department Children´s Hospital (HUS)
Division of pediatrics

Associate professor Annika Janson
Karolinska Institutet
Department of Women´s and Children´s Health
Division of pediatric endocrinology

Associate professor Vladimir Lj Lazarevic
Lund University
Department of Laboratory Medicine
Division of Stem cell research

To my family and friends

Popular science summary of the thesis

Cancer will affect most of us in one way or another. If we are not victims ourselves, it is almost certain that someone in our close proximity will fall ill – a beloved family member or a close friend. Even though survival rates constantly increase, it remains a life-threatening disease that profoundly impacts one's life and serves as a reminder of how fragile life is. Unfortunately, children also get cancer, even though more seldom, and they are more likely to survive. In Sweden, approximately 300 children are diagnosed with cancer annually, with acute lymphoblastic leukemia (ALL) being the most common form—a bone marrow cancer that demands long and burdensome chemotherapy (anti-leukemic drugs) lasting up to 2.5 years. Outcomes have improved significantly over the last 50 years, and today over 90% of the children survive. Nevertheless, there is room for improvement, and the patients are paying a high price with many treatment-related side effects mainly during the treatment, but also later in life. To optimize treatments to further improve survival and to limit side effects, it is important to identify and better understand why some patients have worse outcomes.

There have been reports suggesting that children and adolescents with unhealthy weight, including overweight and severe overweight, or obesity in medical terms, face lower survival rates and an increased burden of side effects, compared to healthy weight children, during ALL treatment. However, the results were conflicting and the reasons for the poorer outcomes were not clear. This thesis therefore seeks to fill an important gap in our knowledge by investigating how obesity, but also underweight and overweight, affect both children and young adults with ALL. This knowledge may help us to improve the possibilities of treating and curing these patients.

With comprehensive data from a total of 2787 children and 416 young adults (between 2- 45 years) with ALL in the Nordic region, including Estonia and Lithuania, we have examined how Body Mass Index (BMI), a measure based on weight and height to identify an unhealthy weight status, affects patients during ALL treatment. We have explored how unhealthy BMI, in comparison to healthy weight, impact on relapse risk, survival and occurrence of treatment-related side effects in both children and young adults. Furthermore, in children, we have studied how BMI changes during treatment, as well as how BMI influences the levels of methotrexate in their blood, an important drug in ALL treatment.

Our studies confirmed that obesity (BMI equivalent >30 kg/m^2) significantly increases the risk of relapse in older children aged 10-18 years with ALL, resulting in a much poorer survival rate of only 60% for this age group. Additionally, older children with obesity face an increased risk of treatment-related side effects. Both underweight and overweight conditions also raised the risk of relapse, although to a lesser extent than obesity. Interestingly, we did not observe a clear impact of BMI on survival in younger children aged 2-10 years. However, we could conclude that they were at a higher risk of being overweight at the end of treatment. For young adults, severe obesity (BMI > 35 kg/m^2) increased the risk of relapse compared to healthy weight adults, although it did not lead to an increase in side effects. We could not observe an significant impact of BMI on the treatment with methotrexate. Yet, children with significant weight loss before their methotrexate treatments had higher concentrations of methotrexate in their blood, which may lead to a greater risk of methotrexate-related side effects.

Overweight and obesity are growing problems in our society – leading to increasing patient numbers with these challenges. Our results, showing a higher risk of relapse, especially in older children with unhealthy BMI, indicates a less successful treatment of these patients. This may be the result of under-treatment, due to concerns of side effects or incorrect dosing, but also due to a reduced effect of the treatment on the leukemia cells, independent of the dose. There is a fine balancing act to intensify the treatment in these patients without causing more toxicity. Therefore, there is a need for more individualized treatment. This thesis also highlights that further research is warranted to study the impact of different dosing strategies and how unhealthy weight affects leukemia cells during treatment. At the same time, it is important not to forget that unhealthy weight problems can be dealt with in several ways. With improved diet, physical activation, and additional treatment approaches, we may reduce the adverse effects that unhealthy weight has on survival and side effects during treatment.

In conclusion, our research has contributed to an increased understanding of the risks associated with unhealthy BMI in children and young adults with ALL. We hope that, based on our findings, future ALL treatments can be better optimized for these patients, thereby contributing to both better survival rates and the limitation of side effects.

Populärvetenskaplig sammanfattning

Cancer berör många av oss på olika sätt. En kär släkting, en nära vän, eller vi själva insjuknar. Cancer påverkar hela tillvaron och blir en påminnelse om hur skört livet är. Barn skonas inte, men insjuknar betydligt mer sällan. Den vanligaste cancerformen hos barn är akut lymfatisk leukemi (ALL), en cancer som angriper skelettets benmärg. ALL är en livshotande sjukdom som kräver en lång och påfrestande behandling med cellgifter (cytostatika) under två till två och ett halvt år. Behandlingen har utvecklats avsevärt under de senaste femtio åren, och idag överlever fler än 90 procent av barnen. Nu är utmaningen att bota ännu fler barn, och samtidigt minimera biverkningarna under och efter behandlingen. För att bota fler med ALL är det viktigt att identifiera och förstå de faktorer som påverkar varför vissa patienter har sämre överlevnad än andra.

Tidigare studier har visat att barn med övervikt eller fetma har sämre överlevnad och mer behandlingsbiverkningar jämfört med normalviktiga, men orsaken till detta samband är okänd. Andra studier har inte kunnat påvisa någon tydlig koppling mellan kroppsvikt och prognos. Syftet med detta projekt är att fylla detta kunskapsgap, genom att närmare studera hur och varför övervikt och fetma, men också undervikt påverkar barn och unga vuxna med ALL.

Vi har använt Body Mass Index (BMI), som är ett mått baserat på vikt och längd, för att bedöma vilka som har undervikt respektive övervikt i våra studier. Med hjälp av information från register över totalt 2787 barn (<18 år) och 416 unga vuxna (18-45 år) med ALL i Norden, Estland och Litauen, har vi undersökt hur olika BMI-nivåer påverkar risken för återfall, biverkningar och minskad överlevnad. Hos barn har vi även studerat hur BMI förändras under behandlingen, samt hur undervikt och övervikt påverkar behandling med cellgiftet Metotrexat, en av grundstenarna i behandlingen av ALL.

Vi har kunnat bekräfta att framförallt barn med fetma (BMI över 30 kg/m2) har en påtagligt ökad risk för återfall i ALL och därmed försämrad överlevnad, jämfört med normalviktiga barn. Hos äldre barn mellan 10 och 18 år var fetma vid diagnos associerat med ökad förekomst av behandlingsbiverkningar och återfall i ALL, med en överlevnadschans på endast 60 procent. Även underviktiga (BMI under 17 kg/m2) och överviktiga (BMI 25-<30 kg/m2) barn i denna grupp påverkades negativt. I de yngre åldrarna (2–10 år) såg vi inget tydligt samband mellan BMI och överlevnad respektive biverkningar, vilket var överraskande. De yngre barnen hade däremot en betydligt större risk att vara överviktiga när behandlingen avslutades. Hos unga vuxna (18-45 år) var det framförallt de med mycket högt BMI (> 35 kg/m2) som hade ökad risk för återfall i ALL, men här såg vi ingen ökad risk för behandlingsbiverkningar. När vi undersökte BMIs effekt på Metotrexatbehandling, kunde vi inte se någon tydlig påverkan. Däremot verkade påtaglig viktnedgång inför start av själva Metotrexatbehandlingen bidra med ökad risk för höga koncentrationer av läkemedlet i blodet, vilket kan öka risken för biverkningar.

Övervikt och fetma är växande problem i vårt samhälle. Våra resultat visar att återfallsrisken i leukemi var som högst hos äldre barn och unga vuxna med ohälsosam vikt, framförallt fetma, vilket indikerar att de inte fått optimal behandling. Några av förklaringarna kan vara felaktig dosering utifrån kroppsbyggnad, eller minskad dos av rädsla för biverkningar. Även en försämrad behandlingseffekt på leukemicellerna hos dessa patienter, oberoende av dosering, kan vara en orsak

till den sämre prognosen. Att öka behandlingsintensiteten som ett alternativ skulle medföra en ökad risk för behandlingsrelaterade biverkningar.

Vägen framåt kan vara en mer skräddarsydd behandling, men också en förbättrad kunskap om doseringsstrategier och hur ohälsosam vikt påverkar direkt på leukemicellerna. Viktigt är också att komma ihåg att den numera konstaterade riskfaktorn ohälsosam vikt i viss mån kan påverkas. Genom koståtgärder och mer fysik aktivitet under behandlingen, finns en rimlig förhoppning om att förbättra prognosen.

Sammanfattningsvis har vår forskning bidragit till en ökad förståelse för riskerna med högt BMI hos barn och unga vuxna som behandlas för ALL. Vi har inte kunnat besvara alla frågor, men förhoppningen är att våra resultat kan användas för att optimera behandlingen av dessa patienter, med både bättre överlevnad och mindre biverkningar som resultat.

Abstract

Background: Overweight and obesity are growing health problems. Obesity has been associated with both a higher risk of contracting cancer and increased cancer-related mortality in adults. The impact in children with cancer, and more specifically with acute lymphoblastic leukemia (ALL), is less explored. Body mass index (BMI) may be an additional risk factor for poor outcomes that warrants consideration in risk stratification for ALL treatment assignment. This study aimed to retrospectively study the association between BMI and ALL treatment in children and young adults treated according to the Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocols and explore possible factors underlying adverse outcomes.

Methods: Patients with B-cell-precursor (BCP) and T-cell ALL from the Nordic countries, Estonia and Lithuania were included. Detailed data on weight and height at diagnosis, as well as patient and disease characteristics, were retrieved from the NOPHO leukemia registries. In *Study I*, we used data collected retrospectively on children aged 2-<18 years and treated according to the NOPHO ALL92-, ALL2000, or ALL2008 protocols between 1992 and 2016, and for consecutive studies we included patients only from the NOPHO ALL2008 protocol *(Studies II, III and IV)* and also comprised of young adults (18-<46 years, *Study V*). In children, BMI was calculated and converted according to the International Obesity Task Force classification into BMI standard deviation scores (SDS), and age and sex-related BMI cut-offs for thinness, healthy weight, overweight, and obesity. The impact of BMI on the following outcomes in children and young adults were analyzed: event-free survival, relapse, overall survival, and treatment-related toxicity and mortality *(Studies I, II and V)*. In children, mean BMI change between diagnosis and the end of treatment, together with identifying risk factors for weight gain were investigated *(Study IV)*. Further, the relation between BMI and delayed high-dose methotrexate (HD-MTX) excretion was explored using data on HD-MTX pharmacokinetics gathered from medical charts from children treated in Stockholm and Uppsala *(Study V)*.

Results: In *Study I* (n =2558), we explored the impact of BMI on survival outcomes in children. Obese children aged 10-18 years at the time of their ALL diagnosis had higher relapse rate and consequently a more than six-fold increased risk of dying from their disease compared to healthy weight patients. Underweight and overweight were also associated with an increased risk of relapse, compared to healthy weight in this age category. However, BMI had no significant impact on outcomes in younger children aged 2-<10 years. In *Study II,* we compared the risk of specific severe adverse events and treatment delays in different BMI categories in a cohort of 1443 children with non-high-risk ALL. A similar age trend was observed in this study; only older obese children aged ≥10 years had a significantly increased incidence rate ratio for one or more specific severe adverse events, compared to healthy weight children. Older children also had a three-fold higher incidence rate ratio of asparaginase truncation, compared with older healthy weight children. *Study III* shows, that BMI SDS increased for many children during ALL therapy (n=765). An increase in BMI SDS was more prevalent in those who were young (2-<6 years) or underweight/healthy weight at diagnosis, compared to other age or BMI groups. To evaluate how BMI influences pharmacokinetics and associated toxicities, one cornerstone of the antileukemic treatment—HD-MTX—was explored in *Study IV*. The results, comprising 182 children and 1401 HD-MTX courses, indicate that children with substantial weight loss during induction had an increased risk of delayed methotrexate excretion.

The results did not support changed pharmacokinetics of HD-MTX as a contributing factor to decreased survival in overweight and obese children. In *Study V*, the role of BMI on outcomes was further examined in young adults, to explore age-related differences in metabolic status and its impact on outcome. Out of the 416 young adults with non-high-risk ALL, only the severely obese patients (BMI ≥35 kg/m^2, n=234) had inferior event-free survival due to relapses. Severe obesity had no effect on toxicity nor treatment delays compared to healthy weight patients.

Conclusions: In obese patients, the poor outcomes are primarily linked to a higher risk of relapse, which may be related to undertreatment or chemotherapy resistance. When trying to improve survival, there is a fine balancing act between intensifying treatment in unhealthy BMI groups with the potential risk of Increased toxicity. For obese patients with ALL, novel strategies with individualized frontline therapy approaches are needed to reduce toxicity while further improving outcomes. Achieving optimal dosing strategies requires further exploration through pharmacokinetic trials. Furthermore, it is crucial to recognize that nutritional status is a modifiable risk factor, where physical activation and dietary interventions, possibly combined with drugs targeting the metabolic pathways, may contribute to better outcomes.

List of scientific papers

I. **Egnell C**, Ranta S, Banerjee J, Merker A, Niinimaki R, Lund B, Mogensen, P. R. Jonsson, O. G. Vaitkeviciene, G. Lepik, K. Forslund, A. Heyman, M. Harila-Saari, A. *Impact of body mass index on relapse in children with acute lymphoblastic leukemia treated according to Nordic treatment protocols.* Eur J Haematol. 2020;105(6):797-807.

II. **Egnell C**, Heyman M, Jonsson OG, Raja RA, Niinimaki R, Albertsen BK, Albertsen, B. K. Schmiegelow, K. Stabell, N. Vaitkeviciene, G. Lepik, K. Harila-Saari, A. Ranta, S. *Obesity as a predictor of treatment-related toxicity in children with acute lymphoblastic leukemia.* Br J Haematol. 2022;196(5):1239-47. Erratum in Br J Haematol. 2022; Aug;198(3):610.

III. **Egnell C**, Narhinen H, Merker A, Jonsson OG, Lepik K, Niinimaki R, Schmiegelow K, Stabell N, Klug Albertsen B, Vaitkeviciene G, Ranta S, and Harila-Saari A. *Changes in body mass index during treatment of childhood acute lymphoblastic leukemia with the Nordic ALL2008 protocol.* Eur J Haematol. 2022;109(6):656-63.

IV. **Egnell C**, Thorwaldson J, Götzsche Frederiksen G, Linde M, Fermer J, Heyman M, Harila A, Ranta S. *The role of body mass index in high-dose methotrexate pharmacokinetics in children with acute lymphoblastic leukemia*. Manuscript.

V. **Egnell C**, Hallböök H, Heyman M, Wartiovaara-Kautto U, Quist Paulsen P, Schmiegelow K, Griskevicius L, Palk K, Toft N, Overgaard UM, Harila A and Ranta S. *Impact of body mass index on outcome and treatment-related toxicity in young adults with acute lymphoblastic leukemia.* Published online: Acta Oncol. 2023 Sep 19:1-9. https://doi.org/10.1080/0284186X.2023.2258450.

Contents

List of abbreviations

6MP	6-mercaptopurine
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferace
ANC	Absolute neutrophil counts
AYA	Adolescents and young adults
BSA	Body surface area
BCP	B-cell precursor
BMI	Body mass index
CAR-T	Chimeric antigen receptor T-cell
CI	Confidence interval
CDC	Center for Disease Control
CNS	Central nervous system
CR1	First complete remission
CRP	C-reactive protein
DCR1	Death in first complete remission
DEXA	Dual-energy x-ray absorptiometry
DFS	Disease-free survival
EFS	Event-free survival
HD-MTX	High dose methotrexate
HR	High-risk
HSCT	Hematopoietic stem cell transplantation
IOTF	International obesity task force
IGF-1	Insulin-like growth factor 1
IL	Interleucin
IR	Intermediate risk
IRR	Incidence rate ratio
MRD	Minimal/measurable residual disease

MTX	Methotrexate
NOPHO	Nordic Society of Paediatric Haematology and Oncology
OS	Overall survival
PEG	Pegylated
Ph	Philadelphia
SAE	Severe adverse event
SCCR	Swedish Childhood Cancer registry
SDS	Standard deviation score
SMN	Secondary malignant neoplasms
SR	Standard risk
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor
TRM	Treatment-related mortality
ULN	Upper limit of normal
WBC	White blood cell

Introduction

Cancer is the leading cause of death in children and young adults after trauma and injury in developed countries. The survival rates of different cancer types are steadily increasing, thanks to individualized risk stratification, the development of new treatments, and improved supportive care.

As a pediatric hematologist and oncologist, I encounter patients at every stage: from diagnosis, during treatment to years after end of treatment during their follow-up visits at our clinic. Various factors contribute to how patients' cancer journey proceeds; both during and after treatment. The strong wish to identify at-risk patients and to improve and optimize their treatment, supportive care, and through this, their outcome, is a large motivator in my work as a clinician and as a researcher.

Acute lymphoblastic leukemia (ALL) has had markedly improved outcomes over the last decades. Assessment of prognostic risk factors is central in the management of ALL. Prognostic factors stratify patients with ALL into different treatment arms, which aim to provide intensive enough treatment to successfully cure the disease with as few treatment-related toxicities as possible. With improved survival, balancing treatment intensity and risk of severe toxicities without compromising cure rates is getting more challenging. This is even more problematic in children with unhealthy BMI due to the influence of body composition on the distribution of anti-leukemic drugs and the metabolic effect of adipose tissue on leukemia cells and their surroundings. Having an unhealthy BMI may therefore contribute to treatment-related toxicity and poorer outcomes. BMI at diagnosis, as a surrogate for metabolic status, is readily available but not considered in treatment stratification.

In this thesis, I have focused on exploring the effect of BMI, especially the effect of obesity, on survival and risk of toxicity during treatment, as well as on pharmacokinetics in children with ALL. To better understand the effects of metabolic status on outcome in different age groups we also studied the effect of BMI in young adults.

The aim was to gain insights regarding the possible impact of weight and body composition (BMI), in the treatment of ALL in children and young adults. We also wanted to raise the awareness of the possible risks associated with obesity in this context, since overweight is a potentially modifiable/preventable factor. Lastly, we also considered the possibility of defining rational possible interventions based on our findings.

1 Literature review

1.1 Historical Background of ALL

In the 1840s, case reports emerged detailing patients experiencing fever, weight loss, and abdominal swelling. Blood tests revealed abnormal white blood cell counts, a discovery that prompted Rudolf Virchow to formally classify this condition as leukemia in 1847[1]. Virchow, along with other eminent physicians, paved the way with their groundbreaking discoveries related to leukemia. However, this did not immediately lead to effective treatment. In the 1940s, the first folic acid blocker was introduced as a new drug and, was further developed into the medication methotrexate, which is still a back bone in the leukemia treatment. As the science of chemotherapy advanced, researchers began to combine chemotherapies, as new medications arrived, raising the possibility of a cure, but most patients did not survive beyond a year of treatment. It was in the late 1960s that the landscape began to shift significantly. Multidrug chemotherapy still used today, together with prophylactic treatment for the central nervous system (CNS), yielded remarkable cure rates, surpassing 50%[2]. From early on, successful cooperative groups were formed, and clinical trials began to draw from larger sample sizes of affected children. Over the past few decades, there has been an impressive improvement in the overall survival (OS) of children with ALL. From survival rates of less than 10% in the 1960s, we are now seeing figures approaching over 90% in developed countries[3-6]. Increased knowledge of the underlying biology, development of more effective chemotherapeutic regimens, and advances in supportive care have enabled this improvement[4,7-9].

1.2 Acute lymphoblastic leukemia

ALL is the most common form of childhood malignancy, with a mean annual incidence rate between 2-4 cases per 100,000 children under the age of 20 years, but it also strikes adults of all ages[10]. The incidence curve of ALL has a bimodal distribution with a peak in children aged 1-4 years and again in adults > 55 years[11]. Males develop ALL more often than females at a ratio of 1.2:1[12].

ALL arises from the proliferation of malignant hematopoietic lymphoid stem cells in the bone marrow, often invading the blood and occasionally extramedullary sites such as the central nervous system CNS. Accumulation of leukemic blasts in bone marrow leads to disturbances in normal hematopoiesis[13,14]. Patients with acute leukemia are highly susceptible to infectious complications; due both to the disease itself and to chemotherapy-induced immunosuppression. Unfortunately, treatment-related death occurs, and a significant number of patients relapse. In results presented in the NOPHO ALL2008 protocol in children and young adults aged 1-45 years, the 5-year incidence of relapse was 10%, while 3% of patients died in complete remission, with relapse and death rate increasing with age[4].

To improve cure rates and minimize therapy-related morbidity and mortality, several countries have joined their efforts and designed common ALL treatment protocols, which also include clinical trials. One such consortium is the Nordic Society of Paediatric Haematology and Oncology (NOPHO), which has designed the Nordic ALL treatment protocols discussed in this project.

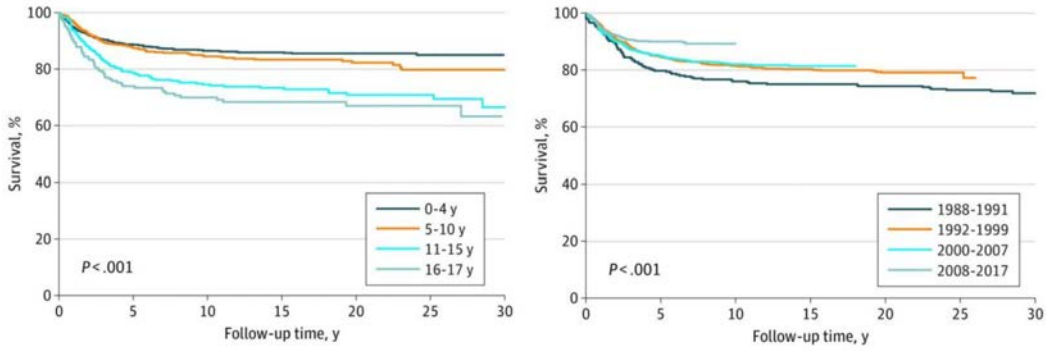

Figure 1. Kaplan-Meier Survival Curves for (ALL) in Sweden from 1988 to 2017.
Y, years. *Source: Modified from Björk-Eriksson et al. Mortality Among Pediatric Patients with Acute Lymphoblastic Leukemia in Sweden from 1988 to 2017. JAMA Netw Open. 2022 Nov 1;5(11):e2243857*[15]*. Permission was granted from the journal.*

1.3 Prognostic factors in ALL treatment

Risk-adapted treatment strategies are the foundation of ALL treatment. The goal is to provide patients with treatments intensive enough to cure leukemia with as few treatment-related toxicities and deaths as possible.

Historically, age (infant or >10 years), a high white blood cell (WBC) count, T-cell ALL immunophenotype, and extramedullary involvement in the CNS at the time of diagnosis have been the main adverse prognostic factors. However, the impact of these factors has somewhat diminished thanks to contemporary risk-adapted therapy[16,17].

Adolescents (from 10 years) and young adults (AYA) generally have worse outcomes (Figure 1) than younger children aged 1-9.9 years, treated with pediatric protocols attributed to less favorable cytogenetics[18-21]. A high WBC count at diagnosis often correlates with a more aggressive disease and poorer outcomes[20,22,23]. Children with BCP ALL tend to have superior outcomes compared to those with T-cell immunophenotypes. The difference, to some extent, is due to less favorable genetic subtypes and higher drug resistance in T-ALL, as well as immunophenotype with T-cell ALL which often present with high-risk clinical features [5,24].

In addition to clinical features, the genetic characterization, and cytogenetics of ALL are mandatory in risk stratification. Among the most common chromosomal subtypes in children with ALL are hyperdiploidy (>50 chromosomes) and ETV6-RUNX1 (chromosomal translocation t(12;21), both associated with favorable outcomes. There are also subtypes associated with poor or intermediate outcomes; KMT2A gene fusions, near-haploidy (<30 chromosomes), low hypodiploidy (30-39 chromosomes), and intrachromosomal amplification of chromosome 21 (iAMP21)[25,26]. The number of novel genetic subgroups with a potential prognostic impact or implications for targeted therapy is increasing, and whole-genome sequencing (WGS) in the diagnostic setting is becoming an important part of diagnostics in development countries.

The most significant prognostic factor, together with genetic markers, is early response to initial treatment. Minimal residual disease (MRD), determined by flow cytometric immunophenotyping and/or polymerase chain reaction (PCR), measures the remaining leukemic cell population in the bone marrow[23,27].

The most established prognostic factors nowadays in pediatric ALL protocols include age, WBC at diagnosis, immunophenotype, CNS status, cytogenetics, and MRD after induction and consolidation[13,28,29]. Treatment intensity is adjusted in reference to these factors by stratifying the patients into different treatment arms [30].

1.4 ALL treatment

Presenting symptoms and signs of ALL can be unspecific but often include signs of anemia, thrombocytopenia, or neutropenia (pallor, fatigue, bleeding and bruising, infections, and fever) and findings of leukemic infiltration in extramedullary sites such as the spleen, liver, kidneys, lymph nodes and CNS[23]. Most treatment protocols for ALL can be divided into four therapy phases: induction, post remission consolidation, interim maintenance and intensification, and maintenance. Based on the characteristics of the leukemia at diagnosis and MRD after induction and/or consolidation patients are divided into different risk group arms. The goal of induction treatment is complete remission, defined as < 5% blast cells and partially recovered bone marrow. CNS prophylaxis with intrathecal methotrexate (added cytarabine and hydrocortisone for CNS positive patients) continues throughout all treatment phases. Total treatment duration is usually between 2-3 years, depending on protocol.

In the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden), treatment for pediatric ALL is standardized in using common treatment protocols created by the Nordic Society of Pediatric Hematology and Oncology (NOPHO). NOPHO was initiated at the beginning of the 1980s with the creation of a prospective registry including baseline variables, and treatment and follow-up data (NOPHO ALL registry) of all Nordic children with ALL. The registration is performed mainly by pediatric oncologists or research nurses and the registry is generally considered to consist of high-quality data.

The first common treatment protocol for pediatric ALL, NOPHO ALL92, was created in 1992. Subsequent ALL protocols, the NOPHO ALL2000 and ALL2008 protocol, were also randomized clinical trials. With the NOPHO ALL2008 protocol, the collaboration expanded to include two Baltic countries: Estonia and Lithuania. The outcome of ALL improved under the period theses protocols were run. A large range of biological and clinical data emerged and was implemented in the treatment approach. These included cytogenetics, pharmacokinetics, new antileukemic agents, MRD monitoring, data on the most effective therapy for specific subsets, and improvements in SCT strategies. The ALLTogether trial (EudraCT number 2018-001795-38 and NCT04307576) is the present protocol currently in use, launched initially as a pilot study in 2018 and 2019 in the Nordic countries and is now running in a larger European collaboration.

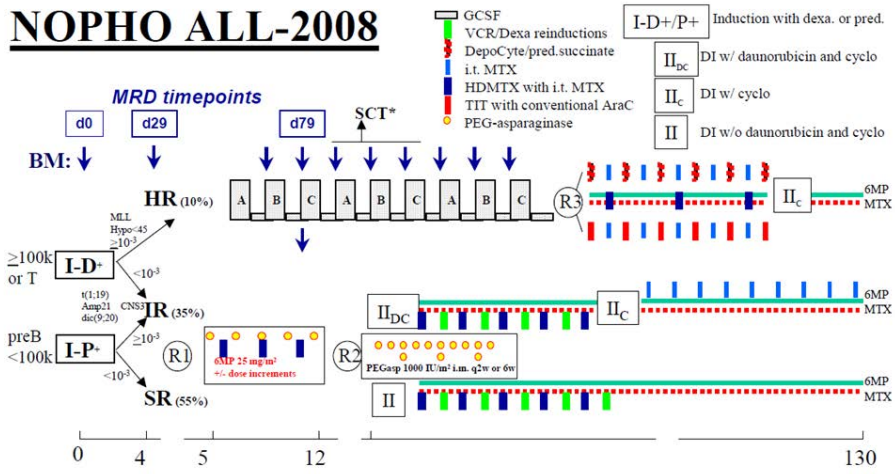

Figure 2. The NOPHO ALL 2008 protocol with stratifications and treatments.
Abbreviations: SR, standard risk; IR, intermediate risk; HR, high-risk; MRD, minimal residual disease; BM, bone marrow; GCSF, granulocyte colony-stimulating factor; VCR, vincristine 2 mg/m^2; HD-MTX, high-dose methotrexate; i.t., intra thecal; TIT, triple intrathecal treatment; I-D, induction dexamethasone; I-P, induction prednisolone; DI, delayed intensification; Cyclo, cyclophosphamide; 6MP, 6-mercaptopurine; R1-R3, randomization 1-3; SCT', stem cell transplantation. *Source: Toft N et al. Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. Leukemia. 2018 Mar;32(3):606-615. Reproduced with permission from Springer Nature*

The latest NOPHO ALL2008 protocol was used for treating children and young adults with ALL between 2008 and 2019 [31,32] (Figure 2). The total duration of the therapy was 2.5 years. At diagnosis, patients were separated into two different induction treatments based on immunophenotype and WBC count. Patients with WBC count > 100x10^9/L and/or T-ALL

received high-risk induction with Dexamethasone on treatment days 1-21, compared to prednisolone treatment on days 1-29 for other patients [32].

The second essential stratification timepoint, treatment day 29, was based on initial risk stratification, cytogenetic alterations and MRD response during induction, separating the patients into standard risk (SR), intermediate risk (IR), or high-risk (HR) groups. Both non-high-risk groups (SR and IR) received conventional consolidation therapy, including oral 6-mercaptopurine and HD-MTX 5 g/m^2, whereas the high-risk group received intensive block treatment, with or without hematopoietic allogenic stem cell transplantation (HSCT). The criteria for HSCT were MRD on day 29 $\geqslant$5%, on day 79 $\geqslant$0.1%, or $\geqslant$0.1% after the second block. The two non-high-risk arms resemble one another; differing only in the addition of anthracyclines/cyclophosphamide in the first intensification phase, a second intensification phase containing cyclophosphamide, and the addition of intrathecal methotrexate during the maintenance phase in the IR-arm (10). Final risk stratification was made after consolidation, on treatment day 79, where MRD values $\geq$ 0.1% assigned patients to the HR-arm. For patients treated in the non-high-risk groups (SR and IR), maintenance therapy included HD-MTX and Vincristine (VCR), and dexamethasone pulses. In addition, pegylated asparaginase was administered during the first 7 months. All administration of chemotherapy was administered based on BSA, however, a ceiling dose of 2.5 mg was used for vincristine (2.0 mg/m^2)[31 4].

Besides demographic data and information on ALL treatment, and response to treatment and outcome, the NOPHO ALL2008 registration also included 22 well-known serious toxicities of special interest (SAEs), registered prospectively[33]. Toxicities were registered during induction and every third month thereafter during treatment for all patients. Other treatment details included were asparaginase administration and the start date of each treatment phase. The definitions of the SAEs used in the study are listed in the attached article, study II[34].

1.5 Primary events

Most patients achieve first complete remission (CR1) and remain in remission without any events, while some patients fail to reach CR1 or die during induction treatment or due to treatment-related death (death in first complete remission DCR1) after induction. The most common primary event is relapse, accounting for 8%-20% over the last three decades in children[7,28,35,36]. Relapse occurs when drug-resistant leukemic clones evolve, or due to inadequate treatment caused by toxicity[37]. After relapse, there is a need for more intensification to overcome treatment resistance, to achieve long-lasting second remission, and patients are already suffering from accumulated toxicity from prior treatments. An additional primary event, also related to treatment toxicity, is secondary malignant

neoplasms (SMN). Event-free survival (EFS) is defined as time from diagnosis to end-of-follow up, relapse, DCR1, or SMN.

1.6 Epidemiology of overweight and obesity

Overweight and obesity is a growing problem worldwide. The World Health Organization (WHO) is describing a global pandemic of obesity with over 300 million obese with increasing prevalence also in low-income and middle-income countries[38]. In high-income countries, obesity is associated with the educational level of the parents, especially the mothers[39]. In children and adolescents, there are similar challenges. In Sweden, in 2020, 13.3% of 4-year-old children were overweight or obese, an increase of 16% in overweight and 31.8% in obese compared to 2018 [40]. Obesity during childhood likely continues into adulthood and is associated with cardiometabolic and psychosocial issues[41,42]. After the COVID-19 pandemic, there are also reports describing increasing weight gain compared to before the pandemic[43,44]. Obesity affects the entire body, in the short, medium, and long term. Figure 3 describes complications associated with obesity from childhood to adulthood.

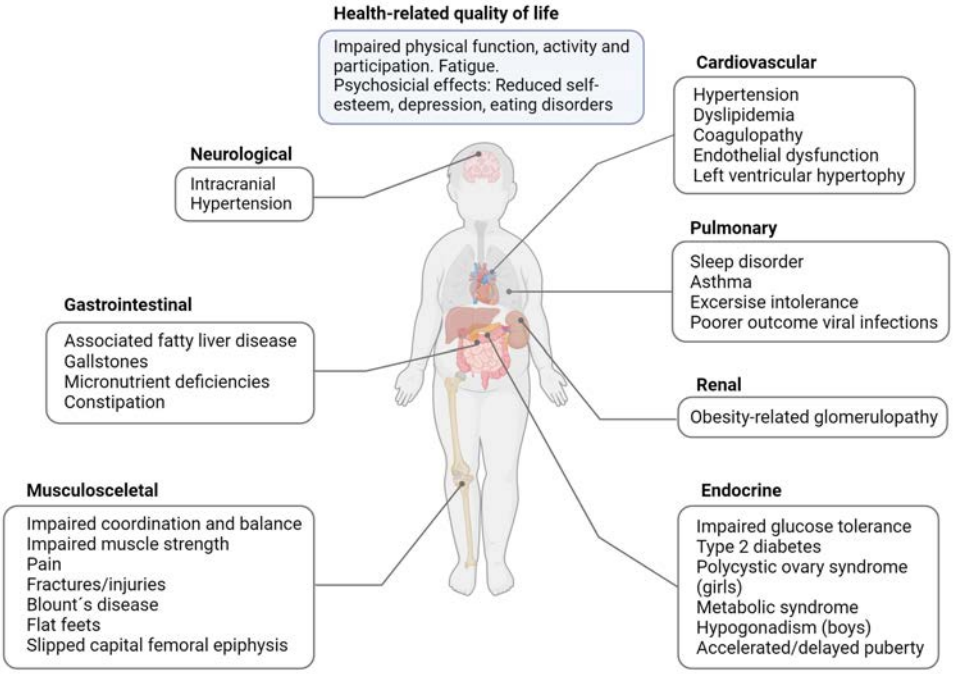

Figure 3. Health complications and comorbidities short-term and long-term, associated with child and adolescent obesity. Created with BioRender.com.

1.7 BMI cut-offs in children

BMI calculated as weight (kg) divided by height squared (m^2) is the most commonly used, measure, used both in clinical practice and in research settings, for monitoring metabolic/(nutritional) status such as underweight, overweight, and obesity. BMI may be misleading, as it does not distinguish between excessive body weight caused by excess fat and that caused by lean mass (muscles)[45,46]. Additional body composition measurements are detailed in section 1.9.3. However, BMI is feasible as a screening tool for defining abnormal nutritional status.

While there is a standard BMI cut-off for underweight, overweight, and obesity in adults, various cut-offs and references are available for children, which complicates comparisons between different studies on BMI. Children change in body size to height ratio due to continuous growth and BMI increases naturally during maturation of the child[47]. To characterize childhood underweight and obesity, an age- and sex-specific reference BMI limit is considered. There are two internationally used BMI-cut-off charts based on reference populations. The WHO reference is based on age- and sex-specific standard deviation scores (SDS)[48,49]. WHO BMI charts and cut-offs are different for ages 2-5 years and 5-18 years, and therefore the prevalence and definitions of overweight and obesity with these BMI charts have minor differences between these age groups (Table 1).

Table 1. Classification of different BMI cut-offs in children

Classification	Low BMI		High BMI	
Cole et al, and IOTF	**≥16 – <17*** "grade 2 thinness"	**≥17 – <18.5*** "grade 1 thinness"	**≥25 – <30*** "overweight"	**≥30*** "obesity"
WHO>5 years	**< –2 SDS** "thinness"		**≥ +1 SDS <2 SDS** "at risk of overweight"	**>2 SDS** "overweight"
WHO >5-19 years	**< –2SDS** "thinness"		**> + 1 SDS – ≤ +2 SDS** "overweight"	**>2SDS** "obesity"
CDC (USA)	**<5th percentile** "underweight"		**≥85th – <95th percentile** "overweight"	**≥95th percentile** "obesity"

*correspond to percentiles that match BMI 17, 18.5, 25, and 30 at the age of 18 years

The other international BMI cut-off reference includes age- and sex-related childhood BMI cut-offs according to Cole et al. for underweight and to the International Obesity Task Force (IOTF) Guidelines for overweight and obesity[50,51]. BMI values at 18 years of age are tracked back to define BMI values for younger ages based on 6 nationally representative data sets. Patients are classified into different BMI groups: thinness grades 1-3 (BMI <16, <17 and <18.5 kg/m^2, respectively); normal weight (BMI 18.5-<25 kg/m^2); overweight (BMI 25-<30 kg/m^2) and obese (BMI ≥30 kg/m^2)[52]. The definition of underweight, overweight and obesity

are also expressed in a SDS framework, based on the same dataset[53]. BMI cut-offs are not available for children below 2 years of age, due to the recommendations that BMI is not used before the age of two years[54].

In numerous studies investigating BMI in children with ALL, applied cut-offs have been taken from nationally-represented data, e.g., in the United States (Centers for Disease Control, CDC)[55-61]. A recent European Childhood Obesity Group recommendation[62] suggests using IOTF[50] and WHO[49,63] definitions to assess childhood overweight and obesity, and definitions by Cole et al.[51] and the WHO for the prevalence of thinness.

1.8 Prognostic impact of BMI in childhood ALL

As the prevalence of overweight and obesity increases in the general population, extreme body weight is a factor more frequently encountered in oncology[64,65]. Obesity has been positively associated both with risk for cancer and cancer-related mortality in general, but also specifically in ALL[66-68]. The association between obesity and the effect on childhood cancer, including its initiation and disease progression, is less studied. Marley et al explored the association of childhood cancer and maternal pre-pregnancy BMI, gestational weight gain, and maternal diabetes and found that maternal obesity and diabetes may be linked to a higher incidence of childhood cancer and especially leukemia and CNS tumors[69]. A similar result was described in a meta-analysis examining the association between the risk of childhood leukemia and increased birthweight (fetal size), which found an increased risk of ALL, suggesting an initiation already in utero[70].

Previous research supports the association between high BMI and adverse prognostic outcome in children with ALL (Table 2). Three recent meta-analyses conclude that high BMI at diagnosis is associated with an inferior OS and EFS in pediatric ALL[71-73]. Two studies demonstrated that high BMI had a negative effect on outcomes especially in children aged 10-17.9 years, suggesting a vulnerability linked to increasing BMI during adolescence[61,74]. However, other studies have failed to show an association between high BMI and outcome [55,56,75,76].

Undernutrition and its importance as a negative prognostic indicator are often cited in pediatric oncology[77-79]. Underweight at diagnosis is common in children with solid tumors but is not described as a prevalent problem at diagnosis of ALL in high-income countries[78]. Studies from low and middle-income countries have reported poorer survival in underweight patients with ALL whereas in developed countries results have been contradictory[59,80,81]. In a Dutch study by den Hoed et al., being underweight at diagnosis of childhood ALL was a risk factor for relapse but was not associated with OS or EFS[80]. In LMIC, where over two-thirds of all children with ALL live, undernutrition at diagnosis and during treatment is more challenging than in high-income countries. In low and middle income countries the overall outcome is poorer compared to high-income countries, due to more

advanced disease at diagnosis, treatment abandonment, and higher rates of treatment-related mortality, mainly due to infections[82].

Table 2. Studies on the association between BMI at diagnosis and outcome of childhood ALL

Reference	Country	N. of patients	Protocol regimen	BMI cut-off	Age, years	Outcome
Hijiya N, Blood, 2006 [55]	USA	621	TOTAL XII, XIIIA, XIIIB, XIV	CDC	1–18	No difference in EFS or OS across the four BMI groups
Baillargeon J, Pediatr Oncol, 2006 [75]	USA	322	-	WHO / CDC	0–<18	No association between OS and EFS in obese compared to non-obese.
Butturini AM, JCO, 2007 [61]	USA	4260	CCG	CDC	2–<20	Higher incidence of EFS and relapse in obese ≥10 years
Orgel E, Blood, 2014 [60]	USA	200	CCG and AALL	CDC	1–<21	Obese had a worse response to ALL treatment by end-induction MRD. Overweight and obese worse EFS
Orgel E, JCO, 2014 [59]	USA	2008	CCG 1966	CDC	1–<21	Lower EFS in obese and underweight for ≥ 50% of pre-maintenance time
Aldhafiri et al. Pediatric Hematol Oncol. 2014 [56]	UK	1033	UK ALL-X	National	2–14.9	No difference in relapse in underweight, overweight, or obese
den Hoed MAH, Haematologica, 2015 [80]	Nether-lands	703	DCOG- ALL 19	National reference	1–17	Increased relapse risk in underweight, no difference in OS or EFS, or in overweight/obese
Martín-Trejo JA, Leuk Lymph, 2017 [83]	Mexico	794	-	WHO / CDC	0–17	Higher risk of death for underweight within the first HR ALL treatment year
Eissa HM, Blood Cancer J, 2017[57]	USA	373	TOTAL XV protocol	CDC	2– <18	Obese had worse OS. No difference in EFS or relapse.
Nunez-Enriques JC, BMC Cancer, 2019 [84]	Mexico	1070	-	CDC / WHO	0–<15	Increased early mortality for overweight/obese. No higher relapse risk (2 years from diagnosis)
Hu et al. Cancer Med. 2023 [85]	China	1437	SCMC-ALL-2005, CCCG-ALL-2015	National (percentiles)	2–17.9	Increased TRM in overweight, but not obese. No effect on OS, EFS, or relapse

Abbreviations: ALL, acute lymphoblastic leukemia; CDC, Centers for Disease Control (USA); EFS, event-free survival; HR, high-risk; MRD, minimal residual disease; OS, overall survival; WHO, World Health Organization.

Studies in children with solid tumors are scarce. Body weight can be misleading in solid tumors, influenced by tumor mass, and thereby underweight can be underestimated[86]. In Wilms tumor with favorable histology in stages I-IV, BMI or height/weight-for-age (in children below 2 years) did not have an prognostic impact on EFS[87]. In a review of the outcome of nutritional status in solid tumors, Joffe et al. concluded that being underweight

(<5th percentile) was associated with worse OS in Ewing sarcoma and osteosarcoma and there was a trend to worse OS in rhabdomyosarcoma. High BMI (> 85th percentile) was associated with increased nephrotoxicity and postoperative complications[88].

1.9 Possible mechanisms on how body composition/nutritional status influences anti-leukemic treatment

Various potential mechanisms explaining the impact of obesity on cancer risk and outcome have been suggested[89]. Obesity is associated with several physiological changes compared to non-obesity including hormonal dysregulation, increased metabolic "fuel", chronic inflammation, and comorbid conditions[90-92]. The impact of these physiological changes on both metabolic and elimination processes, which alter pharmacokinetics and pharmacodynamics, contributes to a complex process ultimately causing chemotherapy resistance. However, the drug-specific impact is not clearly understood or summarized, especially for children and adolescents[93]. Genetic susceptibility and confounding psycho-social and environmental factors may also play a role[94].

An illustration of the complex mechanisms behind the association between obesity and factors affecting ALL outcome is shown in Figure 4.

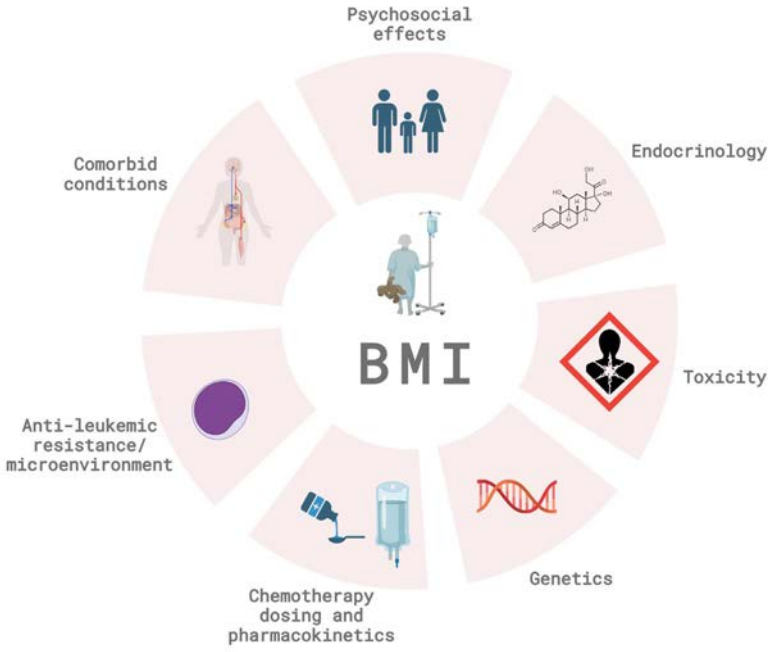

Figure 4. An illustration of the complex mechanisms behind the association between BMI and acute lymphoblastic leukemia (ALL) outcome. Created with BioRender.com

1.9.1 Chemotherapy resistance in obese

Increased body mass is associated with metabolic dysregulation with elevated hormones and growth factors such as insulin, insulin-like growth factor-1 (IGF-1), adipokines (cytokines and hormones in adipocytes), and sex steroid hormones[89]. Hyperglycemia with insulin resistance and increased insulin, IGF-1, and adipokines likely contribute to both ALL incidence and chemoresistance in ALL.

Chronic low-grade inflammation can alter the tumor microenvironment and promote cancer cells through increased concentrations of free fatty acids and pro-inflammatory cytokines[89,95,96]. Adipocytes are active secretory cells and release a variety of factors in the local environment. Pro-inflammatory cytokines, such as interleukin (IL)-6 and 8, IL-1β, tumor necrosis factor (TNF)-α, and macrophage chemoattractant protein-1, but also classical hormones such as leptin, IGF-1, and endothelial growth factor are associated with an increased presence of white adipose tissue[97].

Chemotherapy resistance caused by a direct effect on the microenvironment of adipocytes and leukemia cells is suggested to be one explanation behind observed drug resistance and increased risk of relapse in obese patients[96]. Obese adults have more adipose tissue in bone marrow and in general, therefore obese patients have more potential adipose microenvironments[98]. In in vivo mice models and in vitro models, obesity, through adipocytes, inhibited chemotherapy-induced apoptosis during monotherapy with vincristine[99]. Another animal study with vincristine and daunorubicin demonstrated leukemic blast cell migration into a protective microenvironment in adipose tissue[100]. Ehsanipour et al. reported the provision of a protective microenvironment for leukemic cells by adipocytes through the release of glutamine in the bone marrow, contributing to resistance to asparaginase[101]. Tucci et al. also described in a preclinical study the interaction of adipocytes on the microenvironment of ALL cells, where leukemia cells induced the release of free fatty acids from the adipocytes. Free fatty acids were then utilized by ALL cells as a source of energy which may contribute to chemotherapy resistance[102].

1.9.2 The effect of BMI on pharmacokinetics of antileukemic drugs

Understanding of the pharmacokinetics in obese children is still limited. Consequently, appropriate chemotherapy dosing for obese pediatric patients with malignant diseases is a challenge. Decreasing chemotherapy doses in obese patients may negatively influence the outcome with an increased risk of relapse, and overdosing increases toxicity. In 2015 in a systematic review presented in JAMA Pediatrics on pharmacokinetic studies of children with obesity, only 20 studies could be identified over the last 4 decades, with only 6 small studies based on antineoplastic agents[103]. An extrapolation from studies in adults has been suggested but has indicated the risk of false prediction of clearance and other pharmacokinetic values[93,104]. In children, age also influences pharmacokinetics[105].

The few studies on pharmacokinetics comparing chemotherapeutic agents in obese and normal weight ALL patients are conflicting; studies in underweight patients are scarce. A previous study suggested that a decreased VCR area under the curve (AUC) may be linked with higher relapse risk in children with ALL(216). In the Nordic ALL treatment protocol NOPHO ALL2008, the dose of vincristine was decreased in many obese patients due to "capping" to a max of 2.5 mg with Body surface area (BSA) > 1.0 m^2[2,4,106]. This practice, also present in currently running protocols (capping dose 2.0 mg), is not in line with a review article by Hall et al. on adults, suggesting there might be a need for increased doses of vincristine in obese patients compared to patients at a healthy weight. They also suggests that no dosing alteration may be necessary for obese patients receiving methotrexate, however, a dose decrease might be suitable for cyclophosphamide(106).

Childhood obesity leads to physiological changes which may alter pharmacokinetics. The impact of obesity on pharmacokinetics depends on lipophilicity and how the drugs are metabolized and eliminated[93]. However, pharmacokinetics is also affected by other factors in obese children, such as age, concomitant drugs, and comorbidities. Generally, obese patients are considered to have increased blood volume and cardiac output, an increased distribution volume, and faster clearance compared to healthy weight patients. Obesity can increase the distribution volume due to the high tissue uptake of lipid-soluble drugs[107,108]. An increased glomerular infiltration rate with increasing BMI has also been described, suggesting faster renal elimination in obese children[109]. Obesity is associated with tubular dysfunction. Studies on how tubular dysfunction affects pharmacokinetics are lacking, but they could possibly affect the area under the curve (AUC) and peak concentration of different drugs[93].

The hepatic metabolism of drugs is also affected in obese patients. Non-alcoholic fatty liver disease is common in obese children as well as adults. The effect of obesity on liver metabolism and cytochrome 450 appears to be isozyme-specific with decreasing and increasing activity[110]. The effects on obesity-induced physiological changes that can alter drug disposition is illustrated in Figure 5.

1.9.3 Body composition and dosing

Chemotherapy dose is calculated according to BSA in children and adults. Patients with similar BSA receive the same chemotherapy dose, regardless of body composition and nutritional status and are not developed for use in the obese patients and/or in those with multiple comorbid conditions[111]. In the NOPHO ALL protocols, with the exception of the aforementioned capping dose for vincristine, there are no recommended dose adjustments for obese patients, and in the ALL2008 protocol, a full dose was recommended for obese children and young adults.

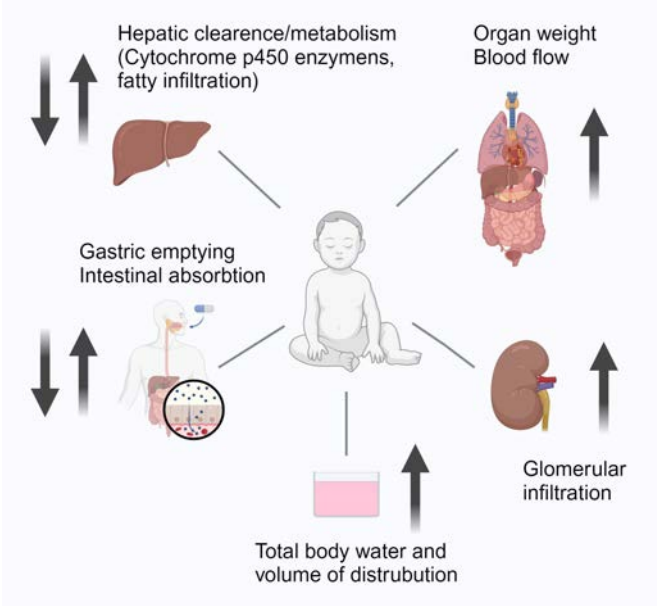

Figure 5. Obesity-induced physiological changes altering drug disposition in children and adolescent. Created with BioRender.com.

Several publications have tried to provide practical guidelines for drug dosing for obese patients[107,109,112]. Other body size measures besides weight or BSA have been proposed to evaluate fat and lean body size in children but can be more challenging to apply in a clinical setting. Direct measures of body composition (difference between bodyweight and fat-free mass) commonly include bioelectrical impedance analysis, underwater weighing/air displacement plethysmography, skinfold measurement, and lastly, dual-energy X-ray absorptiometry (DEXA), which is often described as the gold standard[113]. Of these direct measures, only skinfold measures are easily available in clinical care, which is why indirect measures of body composition have been developed. These indirect measures rely on height, body weight and sex, including BMI, BSA, ideal body weight, percent ideal body weight, adjusted body weight, lean body weight, and predicted normal weight[109]. Currently, BMI is the most commonly used indirect measure of body composition.

1.10 The effect of BMI on toxicity

Therapy-related toxicity in ALL treatment is becoming increasingly important as survival is improving. Identification of risk factors for developing severe toxicity is essential to further improve treatment of ALL. Severe toxicity causes increased morbidity and mortality and often leads to therapy interruptions and dose modifications, which may compromise OS.

Similar to the findings of association between BMI and treatment outcome, the findings of association between BMI and treatment-related toxicities are inconsistent. Orgel et al. found that patients in extreme weight categories were at higher risk for treatment-related toxicities. Obese patients were more likely to have hepatic and pancreatic toxicities, while infectious toxicities were more common among underweight patients[59]. Higher BMI in patients over 10 years of age has been related to a higher risk of CNS thrombosis in ALL, and with higher risk for radiological osteonecrosis[114,115]. Obesity has been shown to correlate with hyperglycemia during induction, which in turn in some studies is associated with poorer survival[116,117]. Low BMI in turn has been associated with hypoglycemia during maintenance treatment of ALL[118]. Obesity increases the risk for spinal epidural lipomatosis, which may complicate CNS treatment, which is especially important in ALL[119]. In contrast, Hijiya et al. observed no association between BMI and toxicities[55]. A single center Danish study with 127 patients by Mogensen et al. failed to show a significant association between BMI and hypertriglyceridemia, osteonecrosis, or pancreatitis[120].

1.11 The effect of BMI change during ALL treatment

Cancer treatment is known to cause large changes in body composition, with challenges with both underweight and overweight patients. Weight gain is common in children during ALL treatment and a significant weight increase is often observed during induction therapy when the patients are receiving glucocorticoid therapy[76,121-127]. Greater weight increase has been observed in patients receiving dexamethasone than in those receiving prednisolones, though the difference has been transient[128,129]. Other factors which impact the nutritional status during treatment are dietary changes, impaired exercise and stress[130]. One relatively small study on 80 patients by Atkinson et al. concluded that girls with standard risk ALL and boys under the age of 4 years at diagnosis may be at the greatest risk of becoming obese during treatment for ALL[131]. In addition, weight gain during induction predicts obesity at the end of therapy[122]. Despite steroids during induction, adolescents were more prone to lose weight during induction compared to younger children[132].

Studies on how change in BMI influences outcome in pediatric ALL patients are scarce. Orgel et al. concluded that obese and underweight patients, who remained in their weight categories over half of the time between the end of induction and start of maintenance, had a significantly higher risk of relapse and death. Normalization of BMI during that period reduced the risk to equivalent to normal weight throughout[59]. Hoed et al. observed that a decrease in BMI during the first 32 weeks of treatment led to poorer OS compared to patients without a decrease in BMI[80].

Whether it is possible to increase OS through interventions for patients with overweight or obesity is unclear. However, Orgel et al. demonstrated potential benefits from caloric restriction via diet/exercise to augment chemotherapy efficacy and improve disease

response[133]. In a previous study by the same author, they also demonstrated an increased EFS in children normalizing their weight during pre-maintenance therapy[59].

1.12 Nutritional status/body composition in survivors

Overweight, obesity, dyslipidemia, and metabolic syndrome are one of the more common disorders diagnosed in survivors of pediatric cancer treatment and are causing an increased risk of late mortality[134-137]. A meta-analysis on the prevalence of overweight and obesity demonstrated significantly higher BMI in ALL survivors compared to the reference population[138]. The increase in BMI was related to steroids, but genetic factors, diet, and physical activity also play a role. Sarcopenia is particularly problematic during ALL therapy[139]. Loss in lean mass is associated with bone mineral density and might therefore worsen the dramatic bone loss described during induction from ALL therapy[140]. In long-term ALL survivors with sarcopenia during treatment, the loss of skeletal muscle mass and strength often preceded the increasing risk of excessive body fat[141]. Brinksma et al. concluded in a retrospective study that at 7 years follow-up BMI z-score had continued to increase and that the prevalence of obesity was 4 times higher compared to rates at diagnosis[142].

A known concern after ALL therapy is neurocognitive dysfunction which has a serious impact on survivors[143]. A longitudinal study on the association of neurocognitive function and BMI during treatment and ≥5 years from diagnosis in 210 survivors of childhood ALL demonstrated that overweight and obese patients had significantly worse neurocognitive outcome. They hypothesize that a rapid initial BMI gain might be a critical factor (due to insulin resistance, hyperglycemia itself, chronic low-grade inflammation)[144].

1.13 Methotrexate and BMI

Methotrexate (MTX) is a key component in the existing treatment regimen for ALL and many other malignancies. In high doses, MTX penetrates the blood-brain barrier and plays an important role in preventing CNS relapses without cranial irradiation[145]. MTX is a chemotherapeutic agent that perturbs the metabolism of folic acid by blocking the enzyme dihydrofolate reductase, thus inhibiting DNA synthesis and rendering affected cells unable to proliferate and synthesize proteins[146]. Administration of HD-MTX (high-dose methotrexate) carries a risk of significant, sometimes life-threatening toxicity. This can in general be prevented by an effective folinic acid rescue. It is mandatory to follow the protocol schedule of hydration, monitoring of plasma MTX levels, and folinic acid rescue.

Previous studies have shown a large inter- and intra-individual variation in MTX elimination[147,148]. The large variation in MTX elimination is difficult to predict and can only to some extend be explained by age, gender, treatment protocol, and germline DNA polymorphisms[149-151]. About 2-4% of patients treated with HD-MTX develop renal toxicity

with severely delayed MTX elimination defined as plasma MTX ≥10 µM at 42 hours after start of the HD-MTX infusion and a 50% increase in plasma creatinine[152,153].

Results from other treatment protocols suggest that patients with fast MTX elimination may achieve unsatisfactory anti-leukemic effect of the drug and have an increased risk of leukemic relapse[154]. Patients with slow MTX elimination have an increased risk of toxicity and are consequently treated with larger doses of folic acid, which in turn can potentially impair MTX effect on later courses and rescue remaining cancer cells[155-157].

Obesity can have an effect on HD-MTX pharmacokinetics and elimination with an altered glomerular filtration and liver metabolism[107]. A previous study comprising 36 patients with ALL aged between 10 and 21 years found an association between obesity and an increased risk for delayed excretion of MTX[158]. In the St. Jude study, intracellular levels of MTX metabolites as well as systemic clearance of MTX, did not differ between 4 BMI groups of 449 patients with pediatric ALL[55]. In adults a higher MTX concentration was observed in patients with high BSA (>2 m^2) or BMI (≥25 kg/m^2)[159]. In a study comparing Capizzi protocol (escalating doses of intravenous MTX with a starting dose of 100 mg/m^2/day 100 mg/m^2, and increasing by 50 mg/m^2 at 10 day intervals for 5 cycles without folinic acid rescue) with HD-MTX in regards to toxicity, lower BMI was significantly associated with MTX-related toxicity in both MTX protocols [160].

1.14 Young adults with ALL and the associations to BMI

Adolescents and young adults (AYA) have specific challenges compared to younger children. The age definition of AYA varies, but most studies include patients aged 15-39 years. They have more poor-risk cytogenetic abnormalities; a higher incidence of Ph-positive ALL, ABL-class rearrangements (Ph-like ALL), and iAMP21, all contributing to a higher risk of relapse[161]. Young adults are therefore more commonly stratified into higher risk protocol, and therefore have more toxicity[32,33]. In the last decades, it became clear that the worse outcome in adults compared to children could not only be attributed to differences in disease biology and treatment tolerance[162]. Pediatric ALL protocols or pediatric-inspired regimens have proven favorable outcomes in AYAs. Yet the potential higher grade of toxicity and consequently higher frequency of not completed treatment is a concern in adults, and there is still room for improvement[162-165]. Advani et al. recognized that a significantly higher percentage of AYA did not complete protocol treatment in pediatric ALL regimen (61%). The most common reason for not completing the pediatric regimen was physicians switching to non-protocol treatment, suggesting a lack of familiarity with the more intensive pediatric regimen[166]. There are also other difficult to quantify issues, such as challenges associated with young adulthood (i.e. living apart from parents, job, education, relationships) that are proposed as potential reasons for treatment discontinuation to clinical trials. ALL is a less

frequent disease in AYAs, and data on this age group are relatively limited, and at least historically, patients in this age group often have inferior access to clinical trials[162].

While obesity is associated both with increased risk of cancer and higher cancer-related mortality in adults [66,67], the results in AYAs on BMI and outcome are conflicting. Stock et al. demonstrated in 318 AYAs, age 17-39, treated with a pediatric regimen that obesity was a risk factor for worse disease-free survival (DFS)[167]. In a recent study on AYAs aged 15-50 years, treated on Dana-Farber Cancer Institute Consortium pediatric ALL, patients who were overweight or obese had worse OS, with a more pronounced negative effect of higher BMI in older AYAs[168]. In contrast, Heibling et al. could not find evidence of BMI having a major prognostic effect on OS in AYAs [169] and in a review by Aleixo et al. high visceral and subcutaneous adipose tissue in patients with hematologic malignancies was associated with better OS[170].

Even less is known about the effect of BMI on treatment-related toxicity in adults with ALL. It is also uncertain whether young underweight or obese adults are more vulnerable to compromised OS, higher relapse rates, or increased toxicity than other age groups. In the on Dana-Farber Cancer Institute study which also studied toxicities, young AYAs, aged 15-30 with overweight/obesity were more likely to experience hepatotoxicity and hyperglycemia compared to those of healthy weight, but this could not be observed in the older AYAs (30-50 years)[168].

2 Research aims

This Ph.D. project aims to explore the effect of BMI, especially the effect of obesity, on survival and risk of treatment-related toxicity, and pharmacokinetics in children and young adults with ALL treated with the Nordic protocols. The ultimate goal is to contribute knowledge that can lead to the development of improved interventions or treatment stratifications, avoiding under- and overtreatment, and thus improve outcomes in this at-risk population through more individualized treatment.

Detailed research aims:

- Explore the impact of BMI at diagnosis on outcome in children treated with NOPHO ALL92, ALL2000, and ALL2008 protocols.
- Study the impact of BMI at diagnosis for the risk of various treatment-related toxicities in the NOPHO ALL2008 protocol.
- Study the change in BMI during treatment with the NOPHO ALL2008 protocol and identify children at risk of increased risk of weight gain.
- Evaluate how BMI influences the pharmacokinetics and the associated toxicity of high-dose methotrexate, in children treated in Stockholm and Uppsala.
- Explore the impact of BMI at diagnosis for outcome and risk of treatment-related toxicity and treatment delays in young adults treated with the NOPHO ALL2008 protocol.

3 Materials and methods

All studies were based solely on data from the NOPHO ALL registry, with the exception of study IV, which included additional data from electronic patient charts. Figure 6 illustrates the data sources of the different studies.

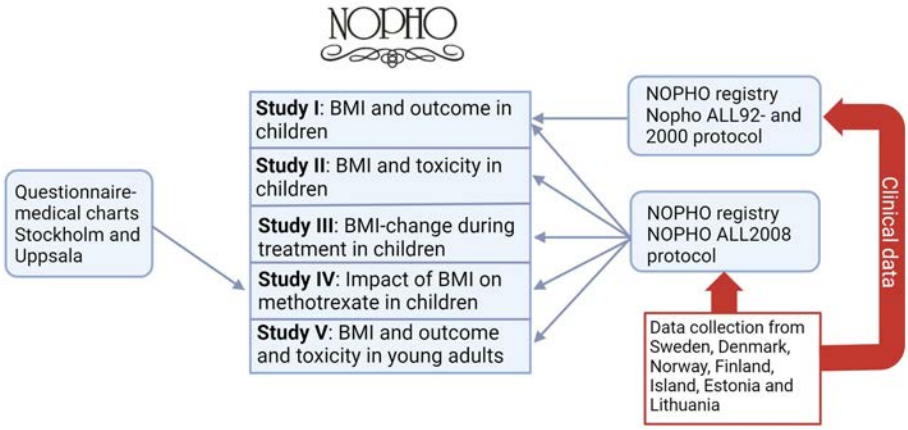

Figure 6. Overview of the Thesis plan. NOPHO, Nordic society of Paediatric Haematology and Oncology. Created with BioRender.com

3.1 Classification of risk groups according to BMI

To define the body composition of the patients, and to identify underweight, overweight, and obese patients, BMI was selected as the best available classification regarding the retrospective design of the studies I-V. Age- and sex-related childhood BMI cut-offs were assigned according to Cole et al. for underweight and to the IOTF Guidelines for overweight and obesity in studies I-IV[50,51]. The patients were classified into different groups: underweight (thinness grades 2), BMI, <17 kg/m^2; healthy weight 18.5-<25 kg/m^2; overweight 25-<30 kg/m^2 and obese ≥30 kg/m^2[52]. The BMI cut-offs used are not available for children below 2 years, and were therefore excluded[54].

In studies I-IV, international age and sex-adapted growth charts (according to the growth charts and cut-off limits IOTF and in the initial results) were also compared with WHO BMI cut-offs to make the results more comparable to other studies. In study V, BMI categorization was made according to WHO cut-offs for adults. Adult patients were classified into five different BMI categories: underweight (<18.5 kg/m^2); healthy weight (normal weight; 18.5- <25 kg/m^2); overweight (25- <30 kg/m^2); obese (class I obesity; 30-<35 kg/m^2); and severely obese (class II obesity; ≥35 kg/m^2)[171].

3.2 Study I

The study covered the three previous NOPHO protocols; NOPHO ALL92, ALL2000, and ALL2008. The NOPHO ALL92 and ALL2000 protocols were open from January 1992 to December 2007. The NOPHO ALL2008 protocol was launched in 2008 and subsequently replaced by ongoing ALLTogether protocol in 2018-2019. The three historical protocols contained same anti-leukemic drugs, but differed in the number of accumulated doses, administration time points, and risk stratification. Cranial irradiation was included in the treatment regimen for patients with CNS leukemia in the very-high-risk groups until initiation of the NOPHO ALL2000-protocol. In NOPHO ALL2008 protocol, CNS-penetrating chemotherapy replaced cranial irradiation. The criteria for group assignment changed over time due to improved MRD monitoring with PCR and flow cytometry, and an increased knowledge of cytogenetic risk stratifying sub-classes [4,7].

3.2.1 Cohort

Patients diagnosed with BCP or T-cell ALL between January 1992 and March 2016 were included. The follow-up period ended in March 2019[172]. Patients with missing data on BMI, pre-treatment more than one week, and non-protocol patients (acute leukemia of ambiguous lineage, Philadelphia positive ALL, mature B-cell leukemia) were excluded (Figure 7). Additionally, children with Down syndrome were excluded due to their known intolerance of antileukemic drugs, worse outcomes and a higher predisposition to overweight and obesity compared to the general population[173,174].

Missing data on BMI at diagnosis (weight and/or height) were more common in older protocols, with 1252/1563 (80.1%) patients in ALL92 and 120/1018 (11.1%) patients in the ALL2000 protocol, compared to 11/1360 (0.8%) patients missing BMI in the ALL2008 protocol. This is probably explained by height and weight not being mandatory baseline register data in older protocols. The group that fulfilled the inclusion criteria but were excluded due to missing BMI did not differ from the study cohort in terms of age, gender, immunophenotype, WBC count at diagnosis, or risk group.

3.2.2 Statistics

The primary outcome was risk of relapse in different BMI categories. The follow-up period began on the day of ALL diagnosis and continued until relapse, HSCT, SMN, death, or end of follow-up (December 2017); whichever occurred first. The Kaplan-Meier method was used to estimate EFS, OS and the cumulative incidence of relapse in different BMI categories.

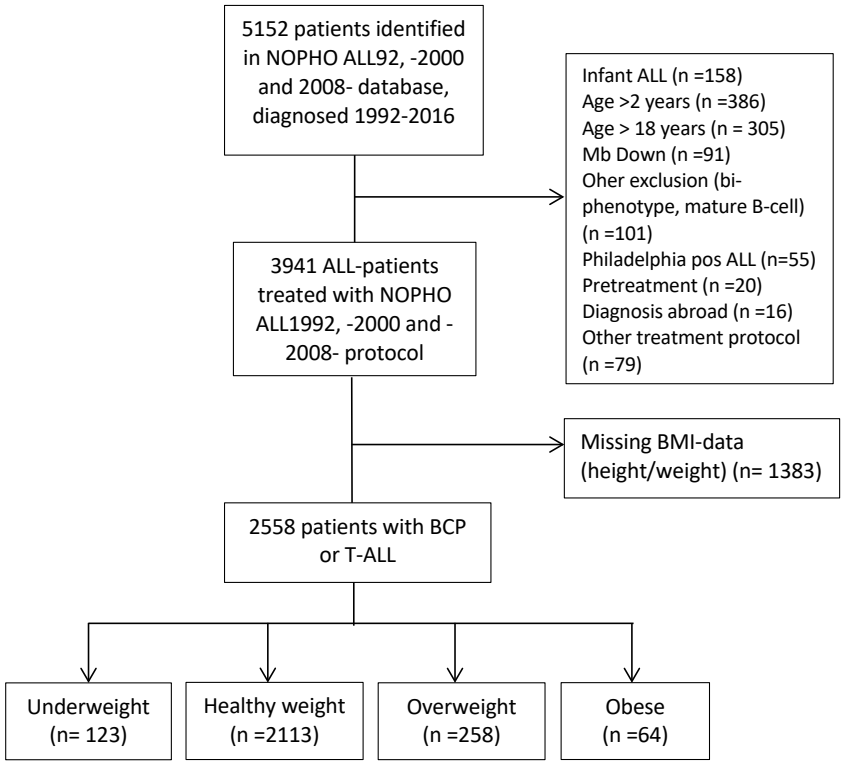

Figure 7. Flow chart for patients included in study I.

The analyses of cumulative incidence of relapse included the competing risks of SMN and death. Overall survival (OS) was calculated from the time of diagnosis to death from any cause. Event-free survival (EFS) was defined as the time from diagnosis until induction death, relapse, SMN, or DCR1. Censoring was performed on the day of transplantation for patients who underwent HSCT in first remission in all analyses. The effect of BMI on relapse, OS, and EFS, but also induction death, SMN, and DCR1 were analyzed in Cox proportional hazard regression analyses. Multivariate models were adjusted for sex, age, protocol (ALL92/2000 and 2008), and risk group (non-high-risk and high-risk). Separate analyses were performed for younger (2-<10 years) and older (10-<18 years) age groups, as well as for non-high-risk and high-risk groups. A Cox proportional hazard model was utilized, using a model of restricted cubic spline (three knots), to visualize the linearity assumption between log hazard ratio of relapse and BMI SDS as a continuous variable. Statistical analyses were performed using SPSS version 25.0 for Windows (SPSS Inc, Chicago, IL) and R version 3.5.0. The association between BMI categories and other categorical variables was explored using the chi-square test. Two-sided p-values <0.05 were considered statistically significant.

3.3 Study II

3.3.1 Cohort description

The study cohort for study II consisted of children aged 2-<18 years, diagnosed with non-high-risk BCP or T-ALL, treated according to the NOPHO ALL2008 protocol between July 2008 and December 2017[34]. Follow-up ended March 2019. Patients from the Nordic countries (Sweden, Norway, Denmark, Iceland, and Finland) and Estonia and Lithuania were included in the study. Patients with high-risk treatment were excluded from this study due to their significantly different block treatment, and in some patients, HSCT. Other exclusion criteria were missing BMI data, patients burdened by other diseases, modifications to treatment (except those arising from toxicity), ALL of ambiguous type, and patients with Down syndrome. In the 2008 protocol, patients with Philadelphia-positive ALL received treatment according to the EsPhALL protocol, and were excluded.

3.3.2 Statistics

The outcomes were the incidence rate ratios (IRR) for different SAEs during treatment and treatment delays from diagnosis until the start of the first maintenance (corresponding to protocol day 134 in the SR arm and 148 in the IR arm). A Poisson regression model, offsetting the logarithm of time in risk of toxicity, was used to estimate IRRs. Adjustment was made for age, considering the well-known increase in the risk of toxicity with advancing age. All patients were censored at the time of early relapse, death from any cause during treatment, and/or the end of therapy (2.5 years). The median follow-up for survivors was analyzed using the reverse Kaplan-Meier method. The proportions of toxic events and clinical patient characteristics were tested using the chi-square test or Fisher´s exact test. Linear regressions of BMI SDS and its correlation with the IRR of SAEs, adjusted for age, were analyzed and presented as correlation coefficients (r) and p-values. Association with treatment delay and BMI was tested through both categorical analyses in each BMI category and with the correlation coefficient and p-value with BMI as a continuous variable. Statistical significance was set at two-sided p-values <0.05. All statistical analyses were performed using IBM SPSS Statistics version 26.0 for Windows (SPSS Inc., Chicago, IL, USA) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria; version 4.1.0) in the forest plot figure.

3.4 Study III

3.4.1 Cohort description

In study III, children aged 2-<18 years with BCP-ALL or T-ALL, treated according to the NOPHO ALL2008 protocol in the Nordic countries, Estonia and Lithuania were included[175]. The inclusion period was between 2009 (in Sweden from 2008) and 2018. Data on height and weight at the end of treatment were not mandatory registry data but were obtained

through questionnaires completed by healthcare professionals and later entered into the NOPHO registry. Patients with incomplete registration or missing data on BMI, patients with other ALL-protocols (acute leukemia of ambiguous lineage, Philadelphia-positive ALL, mature B-cell leukemia), and patients with Down syndrome were excluded. A total of 126 patients did not complete the end of first-line therapy, and therefore, the BMI at end of therapy could not be determined (41 DCR1, 12 induction failure, 64 very early relapses, and 9 early SMN). Additionally, 99 patients who underwent HSCT in CR1 and were excluded. In total, 801/1566 of eligible patients had missing data at end of treatment. Weight loss was defined as a decrease of >1 BMSDS in this study.

The group that met inclusion criteria but had missing data did not differ from the study cohort in terms of age, gender, immunophenotype, white blood cell (WBC) count at diagnosis, or risk group.

3.4.2 Statistics

The mean change in BMI SDS between diagnosis and the end of therapy was calculated for different subgroups using paired t-tests and compared within the groups using independent t-test and one-way ANOVA. Uni- and bivariate linear regression analyses were used to test the association of BMI SDS with other continuous variables. The chi-square test was used to assess the association between different categorical variables, such as BMI category at diagnosis and at the end of therapy, age class (younger children 2.0-9.9 years, and older children 10-17.9 years), ALL subtype risk group, and sex. Two-tailed p-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 28.0 for Windows (SPSS Inc., Illinois, USA).

3.5 Study IV

In the ALL2008 protocol, 5 g/m^2, methotrexate is administered intravenously at a dose of 5 g/m2 over 24 hours for all risk groups and treatment phases. One-tenth of the MTX dose is given during the first hour, with the remainder administered over the following 23 hours. Intrathecal therapy of MTX is given on the same day as the course. MTX monitoring is mandatory at hours 23, 36, 42, and 48 from the start of the MTX infusion until the MTX concentration is ≤0.2 µM/l. Folinic acid (leucovorin, isovorin, or levofolinate) must be given at hours 42 and 48, and then every 6th hour until the plasma MTX concentration is ≤0.2 µM/L. The non-HR patients receive a total of 8 courses of HD-MTX. The time points for each course and concomitant anti-leukemic treatments are described in Figure 8.

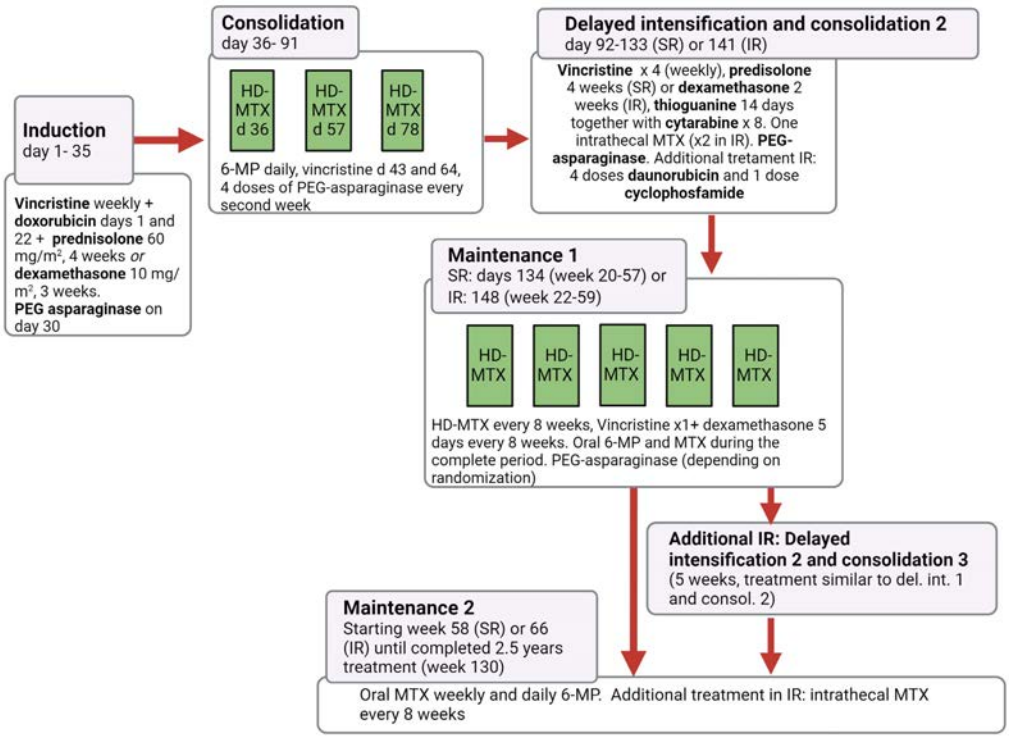

Figure 8. Illustration of the HD-MTX and concomitant anti-leukemic treatment in NOPHO ALL2008 protocol. Abbreviations: 6-MP; 6-mercaptopurine. HD-MTX; high-dose methotrexate, SR; standard risk, OR; intermediate risk. Created with BioRender.com.

3.5.1 Cohort description and data collection

In total, 245 patients aged 2-<18 years and treated with the NOPHO ALL2008 protocol between 2008 and 2019 in Stockholm or Uppsala were identified from the Swedish Childhood Cancer registry (SCCR). Patients treated according to the high-risk arm of the NOPHO ALL2008 protocol, with missing data, or patients for whom data on MTX concentrations could not be retrieved from the electronic medical records were excluded.

Data on clinical characteristics, HD-MTX courses, and related toxicities were collected from the SCCR and electronic medical records. Data collected at diagnosis included height, weight, and creatinine values. During induction, creatinine values and the lowest serum albumin levels were noted. Furthermore, the highest values for alanine transferase (ALT), uric acid, and C-reactive protein (CRP) levels after day 15, were recorded. For HD-MTX courses, information such as infusion dates, creatinine levels, and MTX concentrations were registered. MTX levels of ≥1 to 3.9 µM/L after 42 hours or nontoxic levels ≥72 hours from the start of the infusion were considered mildly delayed. Levels >4.0 to 9.9 µM/L at 42 hours were considered moderately delayed, whereas levels of ≥10 µM/L at 42 hours were

considered severely delayed. Acute nephrotoxicity was defined as a 50% increase in creatinine from baseline during the HD-MTX course, and delayed nephrotoxicity was characterized by increased creatinine within 3 weeks of course start[176,177].

For each HD-MTX infusion, the patient's weight and height at start of HD-MTX course were documented, along with baseline blood counts, creatinine, albumin and CRP values, signs of viral infection, the use of proton pump inhibitors or concomitant antibiotics, and any deviations from the prescribed course. Liver function tests and the presence of fever during the course were also were also recorded. Data collected on toxicity and toxicity-related interventions of interest during the first three courses are described in Table 3.

Table 3. High dose methotrexate-associated toxicities

Toxicities	Definitions
Oral mucositis	Ulceration and/or inflammation of the oral mucosal requiring hospitalization (oral mucositis Grade II and III according to The Common Terminology Criteria of Adverse Effects (CTCAE) v. 5).*
Nephrotoxicity	
Acute	Creatinine increased ≥ 50% during HD-MTX compared to creatinine before start of MTX-infusion.
Delayed	Creatinine ≥ upper Limit of Normal (ULN).*
Hematologic toxicity (myelosuppression)	Neutropenia (<0.5 x 10^9) and/or low platelets and/or low hemoglobin requiring transfusions (of either platelets or erythrocytes) (Anemia and febrile neutropenia Grade III according to CTCAE v. 5).*
Liver toxicity	ALT > 10 x ULN and/or Bilirubin > 5 x ULN.*
Dermatitis	A cutaneous inflammatory reaction.*
Methotrexate-related stroke like syndrome	Focal weakness or hemiparesis, hemisensory deficits, aphasia, dysarthria, dysphagia, and/or diplopia.*

Abbreviations: HD-MTX, high-dose methotrexate; CTCAE, the common terminology criteria of adverse effects; ULN, upper limit of normal; ALT, alanine transferase.
*Within 3 weeks after high-dose methotrexate course.

3.5.2 Statistics

The main outcomes included median MTX concentrations at time points 36, 42, and 60, as well as the median time until reaching a non-toxic level of 0.2 µM/L in different BMI categories and the association of BMI as a continuous variable. Furthermore, the study explored methotrexate-associated toxicities and their prevalence in different BMI categories

Continuous variables were presented as median ± interquartile range (IQR). The chi-square test or Fisher's exact test were used to investigate associations between categorical variables and delayed excretion. For continuous variables between two different groups, the Mann-Whitney test was used, while the Kruskal-Wallis test was applied when there were more than two groups. Linear mixed models were used to evaluate the association between

the natural logarithm of MTX concentration at hours 36, 42, and 60, time to achieving a non-toxic level, creatinine increase, and BMI SDS at each course, considering factors such as age, sex, body surface area (BSA), risk group, and BMI SDS change for all MTX treatments. An autocorrelation order 1 covariance matrix was used to consider the dependencies between MTX concentrations within a single individual. Adjustment variables included BMI SDS, age, sex, risk group, and BMI SDS change in multivariate mixed model analyses. Two-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistical version 28.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

3.6 Study V

3.6.1 Cohort description

In study V, 416 young adults aged 18-45.9 were included, who were diagnosed with Philadelphia-negative BCP-ALL or T-cell ALL, treated according to NOPHO ALL2008 protocol between July 2008 and June 2020. Patients from the Nordic countries (Sweden, Norway, Denmark, Iceland, and Finland) and Estonia and Lithuania were included in the study. The follow-up period ended in March 2023. Patients with missing data on BMI, or missing registry data, pre-treatment more than one week, previous cancer, and non-protocol patients (acute leukemia of ambiguous lineage and mature B-cell leukemia) were excluded. Additionally, patients with Down syndrome were excluded.

3.6.2 Statistics

Outcomes of interest included prognostic outcomes in different BMI categories; EFS, relapse, OS and TRM (any death occurring as the first event in the absence of progressive disease at time of death), as well as risk of toxicities of special interest and treatment delays in young adults diagnosed with BCP ALL or T-cell ALL. Statistical analyses were similar to the outcome analysis in study I, and the toxicity and treatment delay analysis in study II, using the Kaplan-Meier method and multivariable Cox proportional hazards regression models and IRR analyzes. There was no censoring at the time point of HSCT, and HR patients who underwent HSCT were adjusted for HSCT as a time-dependent co-variable in the survival analyses. In the IRR analyses, all patients were censored at the time of early relapse, death from any cause during treatment, HSCT, or at end of therapy. Treatment delay was analyzed as the correlation coefficient and p-value between BMI as a continuous variable and days of delay until the start of first maintenance in non-HR patients and until the start of HR block 4 in HR patients. In the categorical BMI analyses, the median treatment delay for each unhealthy BMI category was compared to the delay in the healthy weight BMI category. An all-comparisons two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics Version 28.0 (SPSS Inc., Illinois, USA) and R statistical software version 4.2.1.

3.7 Ethical considerations

This project is primarily based on registry data from research registries and the NOPHO database and did not involve direct contact with study participants, or have any influence on the patient´s treatment. Nevertheless, ethical issues must be addressed.

3.7.1 Informed consent

Studies I-III and V are registry-based NOPHO studies, and the relevant treatment protocols have obtained ethical permissions for patient registration, which includes collection of toxicity-related data and outcomes. A representative from each NOPHO country is selected for the NOPHO studies and they have verified that appropriate ethical approval is in place for the country. Informed consent for registration and participation has been collected, but with a changed form that has varied over time. Informed consent is obtained at the time of diagnosis, and patients and/or caregivers had the right to withdraw their consent at any time. The purpose of the registration is to improve the decision basis for the optimal treatment of future patients. Patients and/or families are at diagnosis informed in detail of ongoing studies, and that there will also be a future use of the study participants' registry data. However, the future use of their personal data is generally not specified, which may be seen as an ethical problem. A separate procedure with new approval of study participation is time- and cost-consuming, and can also be seen by the research subjects as an unnecessary repetition of previously asked questions. The research subjects and their families have in many cases undergone difficult treatment, which memories they have left behind. Requests for participation in studies, to which they initially believed they had already given consent, can be seen as an unwelcome reminder of a challenging period in their lives. Some of the research subjects are not alive, and the request and obtaining consent from their relatives can be an unwelcome reminder of a past difficult time in life.

3.7.2 Data safety

An important consideration when handling registered data is the protection of the participants' privacy. The participant receives a research number (pseudo-anonymization), and the registry is hosted on certified sites that have been approved by data safety authorities in the countries of participation. All data are presented at a group level, contributing to non-traceable results for any specific study participant.

3.7.3 Approvals from national Ethics committee

Ethical approval for the studies on outcomes (Study I) and toxicity (Study II), the impact of BMI, and the study on BMI changes (Study III) in children with ALL has been granted by the Ethical Committee in Stockholm *(reference number 2018/1888-31)*. An amendment has been approved for the study on outcomes, toxicity, and BMI in young adults (Study V) with ALL *(reference number 2020-01665)*. For the HD-MTX study (Study IV), additional data were

collected from the medical charts of children treated in Stockholm and Uppsala, in conjunction with registry data from the SCCR. This study had a separate ethical approval *(reference number 2021-00825)*, and no new informed consent from the research subjects was required.

4 Results and discussion

4.1 Study I

The cohort consisted of 2558 children, aged 2 to <18 years, treated with the NOPHO ALL92, 2000, and 2008 protocols. Based on IOTF cut-offs, 123 (4.8%) children were classified at diagnosis as underweight, 2113 (82.6%) as healthy weight, 258 (10.1%) as overweight, and 64 (2.5%) as obese. When WHO cut-offs were applied, the number of children categorized as underweight and healthy weight decreased (77 (3.0%) and 1928 (75.4%), respectively), and the number of overweight and obese children increased (426 (16.7%) and 127 (5.0%)). In the older age group, patients were more likely to be overweight or obese or to be stratified into the HR treatment arm. No significant differences were observed in other clinical characteristics.

Because of the age-dependent prognostic risk factors, the cohort was divided into two age groups for analysis: younger children aged 2 to <10 years, and older children aged 10 to <18. The median age at diagnosis was 5.1 years, and the median follow-up time was 6.6 years (range 5 days-23.9 years)[172].

Table 4. Multivariate hazard ratios for relapse and other events according to the IOTF BMI category

	Hazard Ratio (95 %CI)							
	Underweight vs healthy weight	P	Overweight vs healthy weight	P	Obese vs healthy weight	P	Overweight + obese vs healthy weight	P
Age 2.0-17.9 years (n=2558)								
Relapse risk	1.06 (0.62-1.81)	0.85	1.01 (0.70-1.47)	0.95	1.72 (0.98-3.00)	0.06	1.15 (0.83-1.59)	0.39
Overall survival	0.74 (0.27-2.02)	0.56	1.12 (0.68-1.85)	0.66	3.03 (1.66-5.53)	<.001	1.50 (0.99-2.25)	0.05
Event-free survival	1.10 (0.68-1.77)	0.70	1.20 (0.88-1.63)	0.25	2.04 (1.30-3.22)	0.002	1.37 (1.05-1.78)	0.02
Induction death†	1.12 (0.15-8.45)	0.91	0.55 (0.13-2.35)	0.42	1.51 (0.20-11.2)	0.69	0.70 (0.21-2.35)	0.92
DCR1†	0.67 (0.75-2.59)	0.69	1.63 (0.75-3.59)	0.22	2.77 (0.84-9.20)	0.10	2.38 (1.20-4.73)	0.01
SMN†	3.23 (0.71-14.68)	0.13	4.66 (1.71-12.6)	0.003	11.56 (3.18-42.1)	<.001	5.95 (2.47-14.4)	<.001
Age 2.0-9.9 years (n=1980)								
Relapse risk	0.71 (0.35-1.45)	0.35	0.71 (0.42-1.20)	0.20	0.70 (0.26-1.88)	0.48	0.71 (0.44-1.13)	0.15
Overall survival	0.69 (0.22-2.20)	0.53	0.89 (0.45-1.78)	0.75	1.70 (0.62-4.66)	0.30	1.05 (0.58-1.88)	0.88
Event-free survival	0.87 (0.49-1.56)	0.65	0.93 (0.62-1.41)	0.75	1.15 (0.57-2.33)	0.70	0.98 (0.68-1.41)	0.91
Age 10.0-17.9 years (n=578)								
Relapse risk	2.90 (1.24-6.78)	0.01	1.95 (1.11-3.43)	0.02	4.32 (2.08-8.97)	<.001	2.41 (1.49-3.91)	<.001
Overall survival	0.99 (0.13-7.34)	0.99	1.61 (0.76-3.41)	0.21	4.91 (2.20-11.05)	<.001	2.34 (1.29-4.26)	0.005
Event-free survival	2.26 (0.98-5.24)	0.06	1.98 (1.22-3.21)	0.006	4.00 (2.13-7.54)	<.001	2.40 (1.58-3.63)	<.001

The multivariate analyses are adjusted for age, protocol, risk group and sex.
†Due to the small number of events, induction death, death in first complete remission and secondary malignant neoplasm in separate age groups was not conclusive. DCR1; death in first complete remission, SMN; secondary malignant neoplasm.

4.1.1 BMI at diagnosis and outcomes

Obese children had significantly poorer EFS, relapse, and OS outcomes than those with healthy weight. However, after separating the cohort into two age groups, the difference in outcomes were only observed in the older obese children (n=23). Higher risk for relapse was also observed in older underweight children (n=21), but did not affect OS nor reach significance for EFS. The survival outcomes using Cox proportional hazard regression analyses in different age IOTF BMI categories, in comparison to healthy weight children, are presented in Table 4.

When exploring the risk of outcomes in older children with BMI SDS entered as a continuous variable in a cox proportional hazards model using a model of three knots in a restricted cubic spline, a significant association between BMI SDS and the outcomes was found. There was a significant U-shaped risk of relapse and EFS (illustrated in Figure 9).

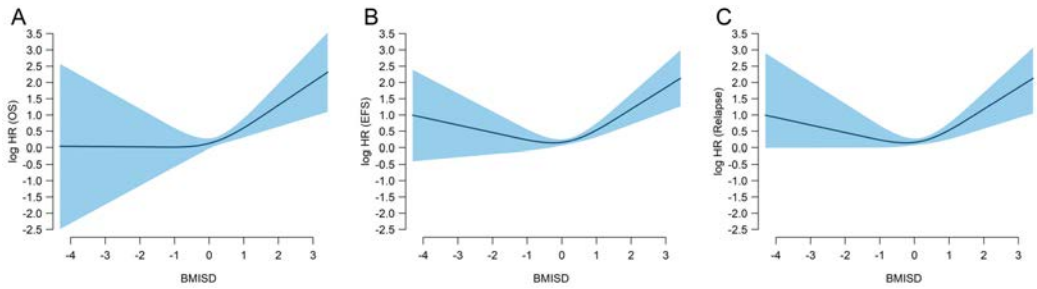

Figure 9. The plot of the association between BMI SDS and **A.** overall survival, **B.** event free survival, and **C.** Relapse in older children. The association can be interpreted such that it is beneficial for both underweight and overweight children to move towards normal weight. The increase of the risk is, however, stronger when comparing higher weight to normal weight. There was also a linear association of BMI SDS and overall survival, but not U-shaped. BMI SDS is written BMISD in the figure.

The adjusted adverse prognostic factors: risk group (non-HR versus HR), age, and protocol (NOPHO ALL92 and 2000 versus 2008), were significantly associated with all outcomes in the different BMI categories using multivariate models. When comparing older protocols (ALL92 and 2000) with ALL2008, the impact of unhealthy BMI on outcome was more pronounced in the ALL2008 than the in the older protocols. When comparing BCP and T-cell ALL, and the impact of BMI in the multivariate cox regression analyses, there were no differences between the immunophenotypes.

Older children with ALL have worse outcomes than younger children[18-21]. However, our study showed no significant difference in the relapse rate between healthy weight younger and older children (11.5% versus 11.4%), as illustrated in Figure 10. The comparable relapse

rate between the age groups in healthy weight children remained consistent even after excluding high-risk patients or when comparing standard-risk (SR) and intermediate-risk (IR) patients separately. One could hypothesize that an important contributing prognostic factor for relapse in older children/adolescents is an age-specific difference related to pubertal changes and higher vulnerability to metabolic and nutritional status within this age category. Unfortunately, we did not have data on pubertal status at diagnosis and the impact of pubertal development during treatment.

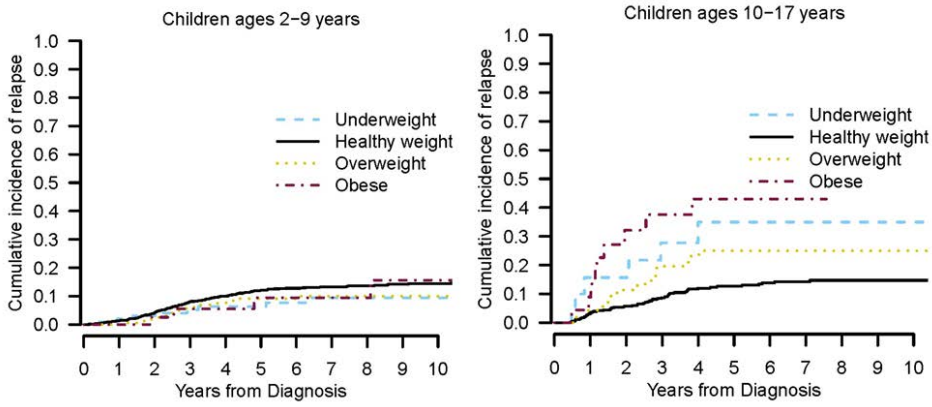

Figure 10. Kaplan-Meier curves illustrating the effect of BMI classification on cumulative incidence of relapse in younger children (age 2.0-9.9 y), and older children (age 10.0-17.9 y). *Source: modified from Egnell et al[172]. Permission granted from the journal.*

Treatment-related mortality and secondary malignant neoplasms in different BMI categories

Death in first complete remission, DCR1 was more frequent in obese children (4.7%, n=3/64) than in healthy weight children (1.5%) aged 2.0-17.9 years (hazard ratio 2.77 [95% CI 0.84-9.2), p =0.10) in multivariate cox regression analyses (Table 4). DCR1 in older children was as high as 8.7% (2/23), but the number of events was too low for statistical conclusions. Both deaths were in SR/IR risk groups. SMN, also a rare event, was significantly increased in both overweight (hazard ratio 4.66 [95% CI 1.71-12.64], p =0.003) and obese (hazard ratio 11.56 [95% CI 3.18-42.12], p =<0.002), which could indicate a genetic predisposition underlying both obesity and cancer.

4.1.2 Comparison to previous studies

Orgel et al. observed an increased risk of positive MRD (≥0.01%) after induction therapy, independent of established predictors of treatment response in obese children, aged 1-21 years with BCP ALL[60]. Sun et al. found that a higher BMI and hip circumference at diagnosis correlated with increased MRD at day 46[178]. Other studies could not find an association of

BMI at diagnosis and early treatment response[57,132]. In our study obesity had no effect on early treatment response.

Our results on the effect of BMI in EFS and OS are in line with previous results. However, our study generally reported higher hazard ratios, which might be attributed to the specific international cut-offs used, including higher cut-offs for defining obesity and overweight[61,72,73].

We confirm that relapse is the main cause of poorer survival in older obese children (39% relapse rate in our cohort), which is consistent with a prior study by Butturini et al[61]. Their cohort of 1000 patients, aged 10-20 years, had a 40% 5-years risk of relapse. Obesity is associated with several physiological changes compared to non-obesity including hormonal dysregulations, increased metabolic "fuel", chronic inflammation, and co-morbid conditions [90-92]. The impact of these physiological changes on metabolic and elimination processes, which alter the pharmacokinetics and pharmacodynamics of treatments, may contribute to a complex process, ultimately causing chemotherapy resistance. This could partially explain the increased risk of relapse, together with dose reductions and treatment modifications due to fear of complications associated with high doses. However, in our study DCR1, related to treatment, was also increased in overweight/obese children.

Underweight older children had a 3-fold increased risk of relapse, with a tendency to worse EFS, but without significant effect on OS. Similar results have been described by den Hoed et. al., with a 2-fold increase of relapse, however without differences between the younger and older children, or in survival. Several factors are likely involved, including reduced immune function, and decreased drug-protein binding that might cause variations in anti-leukemic drug pharmacokinetics[179].

The majority of studies on the impact of BMI on prognostic outcomes in childhood ALL originate from North America and therefore CDC reference for BMI were used[55,57,59-61,75,83,84]. We used IOTF cut-offs and references to define different BMI categories and BMI SDS in children aged 2 -17.9 years. BMI growth references were compared with WHO cut-offs to compare prevalence and outcomes of different BMI categories with different cut-off methods. When using WHO cut-offs, we received similar results, but the risk of worse prognosis was less clear/significant in patients with high BMI, probably due to the lower cut-offs for defining overweight and obesity according to WHO[62]. We also analyzed the results, combining overweight and obese into one group to make the results more comparable with other existing studies that presented their results grouped together[172].

4.2 Study II

The study cohort included 1443 children aged 2 to <18 years at diagnosis treated with the NOPHO ALL2008 protocol, among whom 71 (4.9%) were classified as underweight, 1193

(82.7%) as healthy weight, 139 (9.6%) as overweight, and 40 (2.8%) as obese, at the time of diagnosis, according to IOTF cut-offs[34]. Due to the age-dependent prognostic risk factors, the cohort was separated into two age groups in the analyses; younger children aged 2.0-<10 years, and older children aged 10.0-<18 years, respectively.

4.2.1 Severe adverse events

SAEs in overweight and obese children

When all toxicities of special interest were considered, obese children had more toxicity compared to children of healthy weight (IRR 1.55 [95% CI 1.06–2.25], p =0.022). Similar to study I, where the impact of obesity on outcomes was more pronounced with increasing age, we observed a significantly higher IRR of toxicities only in the older obese children (n =14). Among the older obese children, 85.7% had one or more SAE during treatment, compared to 66.7% of healthy weight older children. The IRR for SAEs did not significantly differ in overweight children compared to healthy weight children. Detailed information and the definitions of the 22 SAEs in different BMI categories is presented in the attached manuscript[34].

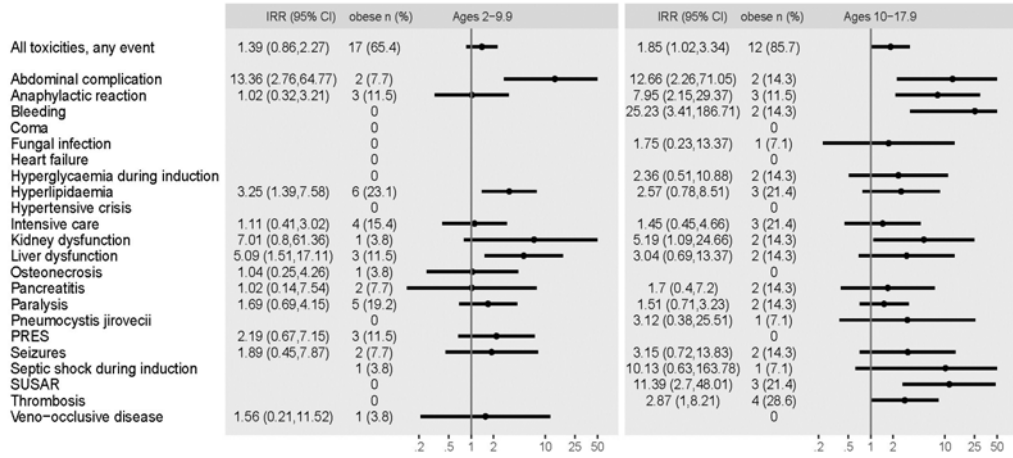

Figure 11. Comparison of incidence rate ratio (IRR) of severe adverse events of special interest between obese and healthy-weight children in different age categories. PRES, posterior reversible encephalopathy syndrome; SUSAR, suspected unexpected serious adverse reaction. *Source: Suppl. figure, Egnell C et al. Obesity as a predictor of treatment-related toxicity in children with acute lymphoblastic leukaemia. Br J Haematol. 2022 Mar;196(5):1239-1247.Permission granted from the publisher.*

In separate analyses of the 22 SAEs, obese children showed an increased risk of liver and kidney dysfunction, hyperlipidemia, abdominal complications, and bleeding, compared to

those of healthy weight. Furthermore, suspected unexpected serious adverse reactions (SUSARs) were more common in obese children. Figure 11, illustrates the 22 SAEs separated into the two age groups. Other studies have reported an increased risk of pancreatitis in obese patients, which was not observed in our study[59,180]. Additionally, higher risk of liver toxicity and hyperglycemia in comparison to healthy weight individuals are well-described in obese children and adults undergoing treatment for ALL[180-183]. Our study showed increased IRR of liver dysfunction, but only a tendency of increased risk of hyperglycemia requiring insulin treatment during induction in obese children. Overall, the incidence of hyperglycemia was relatively low in our study (1.1%, n= 3) compared to 12% in a study by Pollock et al and 16% by Roberson et al[184,185]. This might be explained by differences in the treatment protocols. Our protocol did not combine asparaginase with high-dose steroids during induction, which has been described to contribute to an increased risk of hyperglycemia due to the asparaginase-dependent insulin synthesis[185-188]. Moreover, in our study, hyperglycemia was only registered during induction, which may have contributed to lower registered incidence.

SAEs and underweight

There was also a tendency of increased risk of one or more toxicities in underweight children, especially in younger children (IRR younger children: 1.38 [95% CI 0.99–1.92], p =0.06), compared to healthy weight children. Previous studies have shown an association between poor nutritional status in pediatric cancer patients and an increased risk of toxicity[189,190].

Treatment delays

There was no significant correlation between BMI SDS and treatment duration, and there was no significant difference in treatment delays in the different BMI categories. However, there was a trend towards longer treatment delays during the time period from diagnosis to the start of maintenance-1 in obese older children, compared to healthy weight children (16 and 11 days respectively, p = 0.09). These findings are in line with a study by Butturini et al., reporting no significant treatment delays in obese compared to non-obese patients[61].

4.2.2 Asparaginase truncation and toxicity

In our cohort, asparaginase-associated toxicities, such as thromboses (IRR 2.9 [95% CI 1.0–8.2]), and anaphylactic reactions (IRR 8.0 [95% CI 2.2–29.4]), as well as a higher risk for truncation of asparaginase (IRR 3.5 [95% CI 1.7–7.5]), were more frequent in older obese children compared to those with healthy weight. Of note, there was no significant increased ratio of pancreatitis or osteonecrosis in older obese children. Asparaginase plays a crucial role in the treatment of ALL, and truncated asparaginase therapy has been associated with poorer outcomes[191-195]. Therefore, the higher incidence of asparaginase-related toxicities

may contribute to an elevated risk of relapse in older obese children, warranting further investigation.

Prognostic outcome (unpublished data)

When analyzing survival outcomes in the different BMI categories in study II, including additional 229 patients diagnosed during 2017, the results remained similar in the multivariate cox regression analyses, regarding relapse, EFS and OS in overweight and obese older children. However, in this cohort, younger severely obese children (>35 kg/m^2), had worse OS (hazard ratio 11.6 [95% CI 2.7-50.9], p =0.001) and a tendency to negative impact on EFS (hazard ratio 4.0 [95% CI 0.9-16.6], p = 0.055), but not on relapse (hazard ratio 3.3 [95% CI 0.5-24.5], p = 0.24), compared to the healthy weight group.

4.3 Study III

4.3.1 Change in BMI and height at end of treatment

We studied how BMI changes from diagnosis until end of treatment in a cohort of 765 children aged 2 to <18 years at diagnosis, treated with the NOPHO ALL2008 protocol. Patient characteristics are described in the attached manuscript.

We observed a mean BMI SDS increase of +0.64 SD from diagnosis to the end of treatment. The number of overweight and obese children doubled at the end of treatment. BMI increase was most noticeable among the youngest children with ALL (2 to <6 years), where the number of overweight and obese children increased from 8.8% to 33.4%. A significant decrease in BMI (> -1 BMI SDS) at the end of treatment was observed in 3.5% of patients, with older children being more susceptible to weight loss (9.8%). Only 0.9% of the children with a healthy weight at diagnosis were underweight at the end of treatment.

The mean height SDS at diagnosis was 0.63 and decreased to 0.12 at end of treatment (mean difference -0.51). Loss in mean height SDS was more pronounced in the youngest children (2 to <6 years) with a median decrease of -0.59 SDS. The decrease in height SDS observed at end of treatment is in line with previous studies[80,121]. Of note, Bruzzi et al. showed that the decrease in height was not followed by an appropriate catch-up based on target height, when final height was reached[196].

These results are consistent with earlier studies, but this is the first study investigating BMI change during ALL-treatment conducted in Nordic and Baltic countries[80,121,122,124,131]. Most previous studies are based on treatment protocols with a higher rate of overweight and obesity at diagnosis . Therefore, it was of interest to study the impact of different BMI categories in this cohort. The weight gain during ALL treatment may be permanent. A review on obesity in long-term survivors of childhood ALL showed that obesity after ALL treatment

is prevalent and the BMI z-sore (SDS) is the survivors is substantially higher than in the standard reference population[138].

4.3.2 BMI change and outcome

Study I on the impact of the prognostic outcome and treatment-related toxicities was based on BMI at diagnosis, and we do not know to what extend patients remained in their BMI categories during treatment. It was not possible to analyze the impact of BMI change on outcome under treatment (relapse, EFS, DCR1 and OS) due to lack of BMI at the time of the event. Weight loss during treatment may be associated with toxicity, and therefore a higher risk of dose modifications, which could impact outcome. When only children in CR1 at end of treatment were included in the analysis, there was no association between BMI change and prognostic outcome (unpublished). Previous studies evaluating body composition change during treatment, mostly before maintenance, concluded that the change in BMI or the duration of time in a BMI risk category have an effect on outcomes[59,80]. Orgel et al. showed that for underweight and obese children weight normalization before maintenance mitigated the risk of poorer EFS, as compared to children who were never obese or underweight[59]. Den Hoed et al did not find a difference in outcome between patients with BMI SDS decrease (<0 SDS) and patients with BMI SDS increase at end of treatment[80]. However, children with a BMI SDS decrease during the first 32 weeks of treatment had worse survival. Their study also showed that despite BMI SDS decrease, there was tendency of increased fat percentage assessed by DEXA with predominant loss of muscles (lean body mass). Wadhwa et al. conducted a study on how obesity during maintenance impacts on outcome in children with ALL. They showed that the risk of relapse was higher in children with severe obesity (≤99th percentile) during maintenance, compared to underweight/healthy weight[197]. They concluded that dosing of the maintenance chemotherapy did not explain the poorer outcome. The study was limited by not having access to MRD at the end of induction or BMI at diagnosis.

We also studied whether BMI change under leukemia treatment was associated with pancreatitis, hyperglycemia, osteonecrosis or liver dysfunction, but could not find an association, although children with pancreatitis had lower median weight gains compared to those without pancreatitis (unpublished).

4.4 Study IV

The study cohort was comprised of 182 patients, aged 2 to <18 years, exposed to 1401 HD-MTX courses and treated with the NOPHO ALL2008 non-HR treatment arm. The median age was 5 years, 145 children aged 2-<18 years and 37 aged 10<18 years. When divided into BMI groups, 9 (4.9%) were underweight, 146 (80.2%) had healthy weight, and 27 (14.8%) were overweight or obese (20 (11.0%) and 7 (3.8%), respectively) at diagnosis.

There was a large fluctuation in BMI SDS and changes among BMI categories between the courses (illustrated in Figure 12).

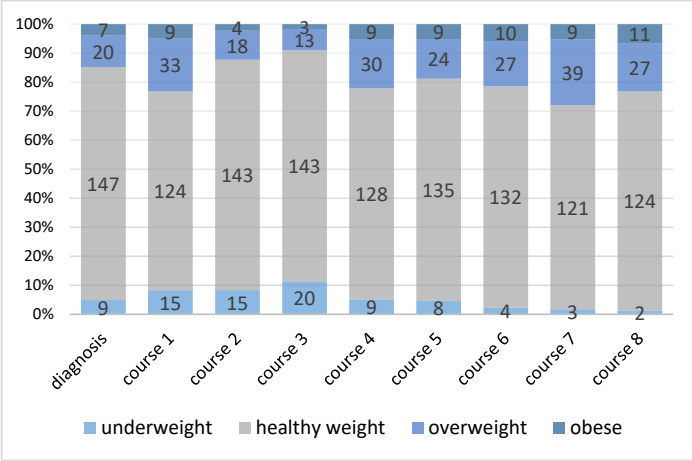

Figure 12. Changes between BMI categories during consolidation and maintenance 1.

MTX excretion was delayed in 18.2% (255/1401) of all HD-MTX infusions at hour 42 (227 mildly, 25 moderately, and 3 severely). We observed a tendency towards an increased risk of higher MTX concentrations and prolonged excretion in children who were obese at diagnosis (Table 5). Mixed model analyses adjusted with the variables BMI SDS at the start of each course, age, sex, risk group, and BMI SDS change, displayed an independently significant pharmacokinetic effect for children with a decrease in BMI SDS (weight loss) before the start of the course. This effect was more pronounced at the first course. Of note, the children who were obese at diagnosis had the highest median BMI SDS decrease from diagnosis until start of the first course, which could explain why obesity at diagnosis associated with increased risk of altered excretion. Older age was also independently associated with higher MTX concentrations at hours 36, 42, 48, and 60, as well as with time to nontoxic level in multivariable analyses adjusted for the same factors ($P < 0.001$, for all analyses).

Mildly delayed MTX excretion was more frequent in patients who were obese at diagnosis: 35.4% of the courses in obese patients had MTX level ≥1 µM/L at 42 hours compared to 18.5% in healthy weight, 10% in overweight, and 22.2% in underweight ($p = 0.003$). Likewise, the proportion of patients with delayed time to nontoxic levels (≥72 hours from start of the infusion) was increased in obese patients (25% in obese versus 15% in healthy weight, $p = 0.026$). The number of obese patients in the cohort was low, and the results were mainly caused by 3/7 obese patients having repeatedly altered MTX excretions.

We investigated whether there is an association between clinical parameters during induction and severely delayed MTX elimination in the first HD-MTX infusion. Except for decrease in BMI SDS, no risk factors during induction, such as hyperleukocytosis, or infections were identified. While infection before start of course did not influence pharmacokinetics, fever during the first course increased the risk of higher MTX concentrations and prolonged excretion, as has been described in a previous study[198]. We lacked data on albumin levels in many patients, and could not analyze the association of albumin levels and BMI loss or altered MTX pharmacokinetics. Some concomitant drugs are known risk factors for altered MTX excretion (e.g., aminoglycosides, proton pump inhibitors, and non-steroidal anti-inflammatory drugs), but the impact of asparaginase on HD-MTX treatment is less well-described. Still, asparaginase, which was given parallel to the HD-MTX infusions during the consolidation phase, decreases albumin levels through decreased hepatic protein synthesis[199].

Table 5. Median methotrexate concentration in different BMI categories at diagnosis and a high-dose methotrexate course.

BMI category at diagnosis	Overall population	Underweight	Healthy weight	Overweight	Obese	P-value
	Median, µM/L (25% and 75% percentile)					
BMI category at diagnosis (all 1401 courses)	182	9	146	20	7	
Median hour 36	1.30	1.30 (1.0, 1.8)	1.30 (0.9, 1.8)	**1.10 (0.8, 1,5)**	**1.70 (1.2, 2.5)**	<0.001
Median hour 42	0.55	0.57 (0.4, 0.8)	0.56 (0.4, 0.8)	0.5 (0.4, 0.7)	**0.79 (0.5, 1.2)**	<0.001
Median hour 48	0.30	0.28 (0.2, 0.6)	0.30 (0.2, 0.5)	0.29 (0.2, 0.4)	**0.42 (0.3, 0.8)**	<0.001
Median hour 60	0.16	0.15 (0, 0.3)	0.16 (0, 0.2)	**0.13 (0, 0.3)**	**0.19 (0.2, 0.3)**	<0.001
Median hours to MTX<0.2 µM/L	60	60 (54, 66)	60 (54, 66)	**60 (54, 60)**	**60 (60, 72)**	0.001
Creatinine increase (median %)	11.5	3.7 (-4.8, 26.3)	12.5 (0, 34.8)	6.7 (-2.9, 1.31)	13.3 (0, 26.8)	0.05
Acute nephrotoxicity (%)	15.5	12.7	15.6	17.3	10.0	0.64
BMI category at course 1	182	15	125	33	9	
Median BMI change from diagnosis	0.07	**-1.16 (-1.6, -0.5)**	-0.03 (-0.5, 0.6)	0.9 (0.1, 1.4)	**1.19 (0.1, 1.6)**	<0.001
Median hour 36	1.40	3.60 (1.3, 4.7)	1.40 (0.9, 2.2)	1.30 (0.9, 1.8)	1.10 (0.8, 6.6)	0.085
Median hour 42	0.65	**1.65 (0.8, 2.2)**	0.62 (0.4, 1.2)	0.64 (0.3, 1.0)	0.40 (0.3, 3.0)	0.037
Median hour 48	0.40	0.90 (0.4, 1.5)	0.39 (0.20, 0.72)	0.33 (0.2, 0.78)	0.20 (0.16, 1.35)	0.11
Median hour 60	0.19	**0.40 (0.2-0.6)**	0.19 (0, 0.3)	0.17 (0, 0.2)	0.10 (0, 0.7)	0.044
Median hours to MTX<0.2 µM/L	60	**90 (60, 114)**	60 (54, 72)	60 (48, 66)	60 (48, 96)	0.019
Creatinine increase (median %)	19.2	23.8 (1, 44)	18.0 (0, 76)	18.8 (4, 39)	31.8 (10, 210)	0.27
Acute nephrotoxicity (%)	23.6	33.3	22.6	18.2	44.4	0.29

Bold numbers are significant values P <0.05 compared to healthy weight
BMI: body mass index, MTX: methotrexate.

The first HD-MTX course, directly following the induction, had a higher incidence of both toxicities and higher MTX concentrations and delayed excretion, compared to the following

courses. Several studies have also shown that the median MTX excretion is lower in the first HD-MTX infusion compared to subsequent infusions [147-149,200]. Sterba et al. reported that the pre-course folate concentration was the principal determinant of peak MTX concentration[156]. It is suggested that folate deficiency is more common in obese children, and adults[201,202]. Decreased baseline folate concentration at the time of the first course in obese patients, before folinic acid rescue, could theoretically contribute to increased risk of MTX-related toxicity. However, this hypothesis could not be confirmed.

4.4.1 Nephrotoxicity and other HD-MTX associated toxicities

In study II, there was an increased risk of SAE kidney dysfunction in obese patients, compared to patients of healthy weight. Renal toxicity can be caused by HD-MTX treatment due to crystallization of methotrexate in the renal tubular lumen, leading to tubular toxicity[146]. When exploring acute or delayed increases in creatinine in this study, no significant difference between BMI categories at diagnosis or with BMI SDS and BMI-change at each course were observed. Zobeck et al. concluded that (BMI < 3rd percentile, according to WHO) at first dose was associated with increased creatinine in pediatric patients during HD-MTX[203]. There was also an observed increased creatinine in children in the BMI range 85%-95%, but not in obese. On the other hand, Khera et al. concluded in a smaller single center study of 45 patients that low albumin(<35 g/L), and not undernourishment (BMI <-2 SDS, according to WHO), was predictive of acute nephrotoxicity[204]. As MTX is a protein-bound drug, the pharmacokinetics of MTX may be significantly altered in underweight patients or patients with weight loss. They point out that in low- and middle-income countries with significant malnutrition rates, malnutrition likely represents an important and modifiable risk factor for MTX-induced toxicity.

Admission for febrile neutropenia ($p = 0.004$), low ANC ($p < 0.001$) and need of platelet- or erythrocyte transfusion ($p < 0.001$) were more common in patients with MTX concentration >1 at hour 42 or nontoxic levels ≥72 hours in the first 3 courses than in patients without delayed excretion. BMI at diagnosis or at the start of the course was not associated with admission for infection, mucositis, or ANC <0.5, nor with the need of platelet- or erythrocyte transfusion after HD-MTX. Except for association between BMI SDS decrease (weight loss) >1 BMI SDS at the first 3 and mucositis (20% in versus 7 % in those with less BMI SDS decrease, $p = 0.02$), no associations regarding BMI SDS decrease and MTX-related toxicities were identified.

4.4.2 Impact on outcome

HD-MTX and its predictive impact on prognosis in different BMI categories were in some ways inconclusive, but the fluctuation in BMI SDS, and especially weight loss may play an important role in altered MTX pharmacokinetics. We observed an increase in median MTX-concentration and prolonged time to non-toxic levels in patients who were obese at

diagnosis, but not in patients who were obese at the start of each course. The increased median MTX concentrations and prolonged time to non-toxic level in obese at diagnosis were mainly caused by three obese patients with repeatedly altered pharmacokinetics. Two of these patients relapsed. There were no reported dose reductions in these patients. Higher MTX concentrations would suggest more efficient treatment of HD-MTX and does not support MTX pharmacokinetics as an underlying mechanism in the worse outcome of patients who are obese at diagnosis, as seen in study I; especially in older children. However, the number of obese children in the study cohort is too small for confident conclusions.

4.5 Study V

In the 416 included patients, aged 18-<46 years, treated with NOPHO ALL2008 protocol, 236 were non-HR and 183 were HR patients. Median follow up was 5.8 years for patients in complete remission.

4.5.1 Outcome, toxicity and treatment delay

Outcome and toxicity in obese and severely obese

The severely obese (BMI ≥ 35 kg/m^2, class II obesity) young adults treated with non-HR protocol had an almost 3-fold increased risk of relapse compared to heathy weight children (hazard ratio relapse 2.98 [95% CI 1.22– 7.27], p =0.02). This increased relapse risk was not observed in underweight, overweight, or obese patients. The increased relapse risk in the severely obese did not impact OS. In the HR patients, there were no associations between the BMI group and OS, EFS, TRM, or relapse rate.

From studies I and II we could conclude that older obese children had an increased risk of toxicity, and an increased risk of relapse. On the contrary, severely obese young adults treated with non-HR protocols, with increased risk of relapse, had a trend towards lower IRR (0.71, p =0.42) for one or more SAE during treatment, with a frequency of one or more SAE during treatment of 50% in severely obese patients compared to 71% in healthy weight non-HR patients. In a small previous study of 66 adolescent and young adults, 21% experienced venous thromboembolisms, comparable with the 22% in our study [205]. Similar to our study, high BMI was not associated with an increased risk of venous thromboembolism.

Outcome and toxicity in underweight patients

No association between EFS, relapse, OS, and TRM was observed in the underweight group compared to the healthy weight group. Although nearly 90% (8/9) of underweight patients treated with non-HR protocol had one or more SAE, compared to 70 % (98/139) in healthy weight patients, the IRR for having one or more predefined SAE did not differ significantly between underweight and healthy weight, adjusted for age. Underweight patients treated

with high-risk protocols had a tendency for higher TRM than healthy weight patients(hazard ratio 3.07 [95% CI 0.63-14.99], p = 0.17).

Treatment delays

There were no significant differences in median time from diagnosis to start of maintenance 1 (corresponding to day 134 (SR) and day 148 (IR)) or the time to start of HR block 4 in the different BMI categories, nor was there a linear association between BMI and median delay.

Dose modifications in young adults

Detailed data on dose modifications, except for asparaginase, were not available for this study. Truncation of asparaginase was suggested to be one possible predictive risk factor for relapse in the obese older children in study II, but this trend was not observed in young adults.

4.5.1 Outcome after relapse and HSCT

The strongest prognostic factors for outcome after relapse are time in CR1 and site, which were not evaluated in our study. Relapse rate, survival after relapse and HSCT in CR1, and DCR1 (independent of time in CR1 before relapse) in different BMI categories at diagnosis are presented in Table 6. Median days from diagnosis to relapse did not statistically differ between BMI categories.

Stock et al. described obesity as a predictor of poor outcome after relapse in an AYA population[167]. However, the survival after relapse depended on risk stratification, and the results should be interpreted with caution. Wieduwilt et al. studied obesity in the context of HSCT in CR1 in AYAs aged 16-39 years and observed an independently inferior OS and EFS and a higher risk for non-relapse mortality as well as relapse of obese patients compared to non-obese patients[206]. Other studies on the subject studying hematologic malignancies and HSCT have yielded conflicting results, suggesting underweight as a risk factor for worse OS and TRM and obesity to also play a negative role, but in one study obesity was even associated with improved survival[207,208]. As relapse rate and DCR1 are rare events, the numbers in our cohort in extreme BMI groups are too small to draw any conclusions.

Table 6 Differences in relapse and death according to BMI category in young adults

Risk stratification	**All patients**	**Under-weight** events (%)	**Healthy weight** events (%)	**Overweight** events (%)	**Obese** events (%)	**Severe obese** events (%)
Relapse all patients	111/416 (26.7)	3/18 (16.7)	64/243 (26.3)	26/95 (27.4)	9/39 (23.1)	9/21 (42.9)
HSCT in CR2 after relapse	51/111 (45.9)	1/3 (33.3)	27/64 (42.2)	14/26 (53.8)	2/9 (22.2)	6/9 (66.7)
Deaths all patients	104/416 (25.0)	3 (16.7)	57 (23.5)	27 (28.4)	11 (28.2)	6 (28.6)
Death after relapse	75/111 (67.6)	1/3 (33.3)	41/64 (64.1)	19/26 (73.1)	9/9 (100.0)	5/9 (55.6)
Death in CR1	22/416 (5.3)	2/18 (11.1)	12/243 (4.9)	5/61 (5.3)	2/39 (5.1)	1/21 (4.8)
Death due to SMN	2/416 (1.3)	0	1/58 (1.7)	1/23 (4.3)	0	0
Induction death	5/416 (1.2)	0	3/243 (1.2)	2/95 (2.1)	0	0
Standard and intermediate risk						
Relapse	56/234 (23.9)	2/9 (22.2)	30/139 (21.6)	12/51 (23.5)	6/23 (26.1)	6/12 (50.0)
HSCT in CR2 after relapse	17/56 (30.4)	0	9/30 (30.0)	4/12 (33.3)	2/6 (33.3)	2/6 (33.3)
Deaths	38/234 (16.2)	0	19/139 (13.6)	9/51 (17.6)	7/23 (30.4)	3/12 (25.0)
Death after relapse	32/56 (57.1)	0	16/30 (53.3)	7/12 (58.3)	6/6 (100.0)	3/6 (50.0)
Death in CR1	6/234 (2.6)	0	3/139 (2.2)	2/51 (4.0)	1/23 (4.3)	0
High-risk chemotherapy						
Relapse	23/81 (28.4)	0	13/46 (28.3)	8/21 (38.1)	1/9 (11.1)	1/1 (100.0)
Deaths	32/81 (39.5)	1/4 (25.0)	20/46 (43.5)	9/21 (42.9)	2/9 (22.2)	0
Death after relapse	18/23(78.3)	0	10/13 (76.9)	7/8 (87.5)	1/1 (100.0)	0
Death in CR1	9/81 (11.1)	1/4 (25.0)	7/46 (15.2)	0	1/9 (11.1)	0
High-risk HSCT						
HSCT in CR1	87/101 (86.1)	4/5 (80.0)	51/58 (87.9)	20/23 (87.0)	6/7 (85.7)*	6/8 (75.0)*
Relapse	32/101 (31.7)	1/5 (20.0)	21/58 (36.2)	6/23 (26.1)	2/7 (28.6)	2/8 (25.0)
Relapse pre-HSCT	7/101 (6.9)	1/5 (20.0)	4/58 (6.9)	1/23 (4.3)	0	1/8 (12.5)
Relapse post-HSCT	25/101 (24.8)	0	17/58 (29.3)	5/23 (21.7)	2/7 (21.7)	1/8 (12.5)
Deaths	34/101 (33.7)	2/5 (40.0)	18/58 (31.0)	9/23 (39.1)	2/7 (28.6)	3/8 (37.5)
Death after relapse	25/32 (78.1)	1/1 (100.0)	15/21 (71.4)	5/6 (83.3)	2/2 (100.0)	2/2 (100.0)
Death in CR1 pre-HSCT	3/101 (3.0)	0	1/58 (1.7)	2/23 (8.7)	0	0
Death in CR1 post-HSCT	4/101 (4.0)	1/5 (20.0)	1/58 (1.7)	1/23 (4.3)	0	1/8 (12.5)

HSCT: Hematopoietic stem cell transplantation, CR1: first complete remission, CR2:second complete remission, SMN: secondary malignant neoplasm.

*One obese patient changed to HR chemo due to toxicity and one severely obese patient with unknown reason for not going to HSCT

5 Strengths and Limitations

One strength of the registry-based studies is the prospective registration and nationwide coverage, including all Nordic countries. The NOPHO ALL registry data is considered to contain high quality data and few patients are lost to follow up. The group is homogeneous and included patients receiving comparable health care services and standardized primary treatment. The endpoints used (OS, EFS, DCR1, and relapse) were the same that have been used in NOPHO countries over many decades. The cohorts were large, enough to enable us to study the different BMI categories. However, a challenge in our studies was the low number of underweight and obese patients, especially after stratification into different age groups, risk groups, or analyses of separate toxicities, which limited the interpretation of the results.

Another strength is that the population is based in Nordic and Baltic countries with a relatively low prevalence of obesity (Northern Europe) and where very few studies have been conducted regarding associations between prognosis/toxicity and BMI. Most studies are based in North America, a population with significantly more diverse ethnicities, and more overweight and obesity. Nordic and Baltic obese patients may differ from obese patients in countries where obesity is more prevalent, and therefore it is important to confirm previous results in our setting.

The major limitation of our project is that the NOPHO ALL registry was not designed to address the issue of obesity and outcome. We used BMI, an anthropometric method, in all our studies for classifying the nutritional status/body composition at diagnosis and at the end of treatment. No BMI data were routinely registered during treatment, except for *study IV*. Furthermore, while BMI is commonly used in clinical practice and in research settings, it may be misleading, as is does not distinguish between excessive body weight caused by excess fat and that caused by lean mass (muscles) or between abdominal or general obesity[45,46]. A better way to evaluate nutritional status would be to include body composition, by for example with DEXA in addition to anthropometric methods. In this retrospective study this was not possible. One study validated the change in BMI z-scores in children during ALL treatment with DEXA and found a significant correlation between BMI z-score and body-fat percentage within the 128 pair of measurements, but the correlation within each individual was not significant[46] as the high prevalence of sarcopenic obesity (gain in body fat percentage with loss in lean muscle mass) during treatment was not reflected in the BMI z-score analyses and large gains in body fat were missed due to concurrent muscle loss. The results imply a risk of under-diagnosing overweight and obesity when using BMI-SD/z-score to evaluate changes in body composition in children with ALL.

Also, since this was a register study, we could only analyze the toxicities of special interest that had been prospectively registered. Other toxicities, such as infections or lower grade of

liver- or nephrological toxicity, which could impair treatment were not included. Similarly, we could not determine whether puberty had an effect on toxicity or outcome in studies I and II, due to missing data on puberty status. Furthermore, especially in *study I* in the old NOPHO ALL92 protocol, the registration of weight and height was not mandatory, and therefore several patients were excluded due to missing BMI data. The older protocols also contained less and had less access to detailed data on MRD-levels and cytogenetics, a central tool for risk group assignment. Further, we did not include children aged 1-<2 years, a significant number of patients, and therefore the results may not apply to the youngest children.

With the exception of asparaginase, data on dose modifications are not registered in the NOPHO ALL registry. Instead, we used treatment delays as an indirect measure of toxicity. We suspect that obese patient had more dose and treatment modifications, but cannot verify this hypothesis with the registry data. In the current treatment protocol, ALLTogether1, that followed after NOPHO ALL2008, there is mandatory registration of dose adjustments exceeding >10 % in each treatment phase. Future studies will therefore better be able to adjust for treatment modifications. This is a major concern in young adults, where both dose modifications and other treatment options are more common.

We did not take ethnicity into account. Children with ALL who are of Hispanic or African origin have had worse reported outcomes[209,210]. The NOPHO protocols contain a relatively homogenous group, but adjustment for ethnicity may further improve the results. Socioeconomic status may also impact ALL outcome: access to care, poor adherence to maintenance, and overall health status can also contribute to poorer outcomes[211]. The increased risk of obesity in high-income countries and its association with lower socioeconomic status may be a contributing risk factor in obese patients[39], while there are challenges also with undernutrition (underweight) in low- and middle-income countries. Health care policies focusing on diagnostic improvements, cancer registration, and newer therapeutics at reduced cost or with insurance coverage are needed in low and middle-income countries.

Data on MTX in *study IV* were collected retrospectively from patients' medical charts. We did not collect data on folinic acid rescue in *study IV*. However, it is reasonable to assume that the higher the concentration and the longer excretion time, the more folinic acid was given. It is suggested that lager rescue doses of folinic acid inhibit the therapeutic efficacy of MTX in later HD-MTX treatments. Clinical trials using different doses of folinic acid have shown a trend to increased relapse rate in pediatric ALL patients receiving higher doses compared to those receiving lower doses[157,212]. Data on two additional factors that may affect the MTX excretion, urinary output (clearance) and urinary pH, were not registered.

6 Conclusions

The impact of obesity in ALL has been controversial. This thesis and previous studies offer convincing evidence that body composition and nutritional status influence outcomes and toxicity during treatment of childhood ALL.

Our first study confirms that an unhealthy BMI at the time of diagnosis has an adverse impact on the outcome. We can conclude that the most pronounced impact of an unhealthy BMI occurs during preadolescence and adolescence. Among older children with obesity, the risk of mortality is nearly five times higher when compared to their healthy-weight peers. The worse OS is primarily due to a higher relapse rate. The influence of BMI on relapse and event-free survival (EFS) is also noticeable among underweight and overweight older children. Importantly, the overall survival and cumulative relapse rate remained similar when comparing younger and older children with a healthy BMI, signifying that an unhealthy BMI at diagnosis represents an independent risk factor for an inferior outcome within this age group.

With a higher rate of relapse, the possibility of stratification to more intensive treatment could be considered. However, in *study II,* we showed that older obese children also experience more toxicity than healthy weight children. Increased toxicity is challenging and may lead to dose modifications, such as truncation of asparaginase in obese children. In young obese adults, there was a tendency toward worse OS, but only severe obesity (BMI >35 kg/m2) was predictive of an increased risk of relapse. Severely obese young adults, in contrast to the older obese children with an increased risk of relapse, did not have a higher rate of toxicity compared to their healthy-weight peers. The results for severely obese young adults suggest that underdosing or dose modifications may be contributing factors to worse outcomes.

Survivors of childhood ALL also have an increased risk of gaining weight, most likely due to steroids and lifestyle changes during the intensive treatment. Younger children are at the highest risk of unhealthy weight gain. As previous studies have indicated overweight persists after end-of-treatment, and interventions to prevent weight gain during treatment are warranted.

Altered pharmacokinetics of HD-MTX was observed in patients who were obese at diagnosis, but obesity at diagnosis was not associated with toxicity or dose modifications. The pharmacokinetics of HD-MTX had the largest impact on children who experienced weight loss before starting the HD-MTX course, leading to an increased risk of higher MTX concentrations, delayed excretion time, and a higher likelihood of developing mucositis. The hypothesis that children with obesity would experience more toxicity and, consequently, more modified HD-MTX treatment was not confirmed.

With the increasing prevalence of obesity worldwide in both children and adults, there is a growing awareness of the impact of obesity on cancer outcomes. Our results, showing higher relapse rates, especially in older children with unhealthy BMI, indicate insufficient chemotherapy, but also a higher vulnerability to chemotherapy with more toxic events. It is a difficult balancing act to intensify the treatment in these patients without causing more toxicity. Therefore, there is a need for more individualized treatment, for both underweight and obese patients. Immune targeting agents such as inotuzumab or blinatumomab into frontline therapy may allow for decreased treatment intensity of conventional chemotherapy, thereby reducing toxicity while further improve outcomes for underweight or obese children and adults with ALL. This project has also highlighted the need for a better understanding of chemotherapy dosing, pharmacokinetics, chemotherapy resistance, and therapeutic drug monitoring, which, in the future, can help optimize chemotherapy regimens for patients with an unhealthy BMI.

It is crucial to remember that nutritional status is a modifiable risk factor. Comprehensive studies involving continuous nutritional assessments from diagnosis, throughout treatment, and during long-term follow-ups are required, so that interventions can be implemented and their effects evaluated.

7 Points of perspective

Historically, nutritional research has not been a priority within cancer cooperative clinical groups[213]. However, with rising prevalence rates of obesity in society, there is increasing interest in how metabolic status impacts patients with ALL. Further insight into the mechanisms behind the adverse outcomes associated with an unhealthy metabolic status is essential to guide future interventions.

Risk stratification and other front-line therapies

With the increased risk of relapse in obese older children and severely obese adults, dose de-escalation therapy is not reasonable, but it is a group that needs special considerations. Is obesity in older children or severe obesity in young adults a new variable that should be considered in risk stratification? Innovative agents, molecular targeting, and immunotherapy—alongside conventional therapy, are promising candidates, and may in the future have a more prominent role with increased use also in front-line therapy, to manage the balancing act between the risk of relapse with inadequate treatment intensity and treatment-related toxicities. Of note, overweight/obesity in children and adult patients with B-ALL has not had a negative impact on the effect of chimeric antigen receptor (CAR) T-cell therapy[214].

Optimization of anti-leukemic dosing

An important research area is optimal chemotherapy dosing, with adapted dosing based on pharmacokinetic or pharmacogenetic factors in patients with different metabolic status. The effect of chemotherapeutic agents, given their more or less narrow therapeutic window, more often than now need to be evaluated with therapeutic drug monitoring. Limited information for adapted dosing of chemotherapeutic agents is available in obese patients, especially in severely obese patients. Dose reductions have frequently been used to limit excess toxicity in obese patients, but with a risk of providing less-effective treatment.

Chemotherapy dosing is based on BSA. However, calculations for BSA are not developed for use in the obese patients, as BSA increases slower in proportion to body fat mass[215]. Dose-capping is commonly used for vincristine, which may result in underdosing. However, a review on pharmacokinetic parameters of anti-leukemic drugs in adults suggests a need for increased doses of vincristine in obese patients[108]. A previous study suggested that a decreased vincristine area under the curve (AUC) may be linked to higher relapse risk in children with ALL[216]. In study II, we observed a higher proportion and increased IRR for truncation of asparaginase in obese children, which warrants further investigation. Asparaginase activity has been measured as part of ALL2008 protocols to detect neutralizing antibodies. The NOPHO leukemia working group has discussed how intramuscular injections of asparaginase may not reach muscle tissue, which could affect pharmacokinetics in adult

patients with very high BMI. Further studies on asparaginase activity and the association with BMI are required. We are planning a collaborative study to investigate asparaginase activity and more detailed asparaginase toxicity in different BMI categories.

The pharmacokinetics of antileukemic drugs is complex and further prospective studies on dose individualization, especially in obese and underweight children and adolescents are needed. Until we have evidence-based guidelines for chemotherapeutic dosing in extreme BMI categories it is important to follow clinical practice and treatment protocols with full chemotherapy, immunotherapy and targeted therapies doses. Obesity should not in itself be the sole base for dose modifications[217].

Cytogenetics and germline mutations in obese patients

Intrinsic biologic features could predispose patients with obesity to more aggressive ALL. The high relapse rate and the association with obesity may be a surrogate marker for an underlying genetic susceptibility leading to more aggressive types of ALL. Mittelman et al. found an association between increased body fat and higher rate of rearrangement in cytokine receptor-like factor 2 (CRLF2r) in older children and adolescents (>10 years), a suspected high-risk subset of B-cell ALL (BCR/ABL1-like) affecting kinase genes [218]. The number of novel genetic subgroups with a potentially prognostic impact or implications for targeted therapy is increasing, which could contribute to improved outcomes in future protocols. Whole genome sequencing of germline DNA is implemented in an increasing number of countries at diagnosis and could add more information on underlying predispositions and genetic susceptibility in obese and severely obese patients, improving our understanding of worse outcomes and increased risk of developing ALL.

Monitoring of body composition at diagnosis, during and after treatment

Regular monitoring during and after treatment for patients at risk of developing metabolic syndrome is important to enable early interventions. Availability of more detailed data on metabolic status/body composition will also make it possible to improve our knowledge on the effect of obesity and underweight in future research. This could be achieved by registering supplementary measures of body composition, especially change in body composition. In a clinical setting bioelectrical impedance analysis (BIA) could be a feasible method for monitoring body composition and fat percentage as well as the development of sarcopenia [219-221].

Interventions during treatment

Obesity is a potentially modifiable prognostic factor. By reversing the physiological changes associated with overweight/obesity with interventions, we can hypothetically improve chemosensitivity, and prevent weight gain during therapy. Nutritional and physical activity (exercise) interventions can be challenging, with decreased adherence under ALL treatment.

Patients and families are hit by sudden life-threatening issues, chemotherapy-associated toxicities, and in older children and adults not seldom fatigue, all of which compete with their interest in ambitious interventions. In general, the treatment of obesity in children and adolescents with lifestyle programs to reduce weight-related comorbidities is described as modestly effective and generally deemed insufficient[222]. Yet, an obesity-intervention (dietary and physical activation) trial during the induction of HR-ALL in children aged 10-21 years showed promising results concerning the reduction of fat mass, increased insulin sensitivity, and early response (MRD) in overweight and obese patients at diagnosis [133]. One ongoing randomized phase 2 study in AYA with B-ALL aims to increase chemosensitivity with personalized nutritional menus and exercise plans (NCT05082519). In a dietary intervention study, feasibility and the impact on weight gain during the initial phases and the common 6 months of ALL treatment were tested. The results were convincing, with good feasibility and no increase in median BMI z-score during induction or over the six-month intervention[223].

With mounting evidence that adipocytes alter the function of leukemia cells and the direct environment, together with the physiological changes of obesity, it is important to identify obesity-induced pathways in the leukemia cell that can be targeted to improve outcome. Ways to target the metabolic obesity-associated pathway have been suggested[224-226]. One example is metformin, which also has potential anti-cancer activity[224]. Metformin has shown leukemia cell growth inhibition in vitro and been tested during induction of relapsed pediatric ALL patients in a phase 1 study[227-229]. Whole-foods plant-based diets and fasting-mimicking diet cycles have also been suggested to have a positive effect on obesity induced pathways during treatment[230,231].

Interventions after treatment

Overweight and obesity often remain and even increase after the end of treatment[141,142]. How can we prevent the effects of the negative metabolic changes caused by the cancer treatment? Survivors of childhood cancer have an increased risk of developing metabolic syndrome[135]. Sarcopenia (loss of muscle mass) is common in children with ALL and can persist after end of treatment leading to a higher risk of metabolic dysfunction[46,135,139]. Physical activity during and after cancer treatment is, therefore, an important tool; especially due to observed increased physical activity among survivors[232,233].

Multidisciplinary approaches are needed. Primarily lifestyle interventions, but also bariatric surgery and anti-obesity medication in older children and young adults are possible treatments. Nutritional education and intervention, and improving physical activity already during treatment may counteract the increased risk of developing chronic metabolic disease[232,234]. Metabolic and bariatric surgery is a standard treatment in severely obese adults and has in a randomized trial proven promising results compared with intensive non-surgical treatments in adolescents, however, longer-term follow-ups are needed[235]. An

increasing number of drugs with significant effect on weight loss together with life-style interventions have been approved as anti-obesity medications in adults, and some have been approved for older children. Drugs i.e., orlistat, bupropion, liraglutide and semagludite, could play an important future role in managing the metabolic late effects of ALL treatment[236,237].

The time has come for us to move from description of the negative effects of obesity on ALL outcomes and move toward intervention.

8 Acknowledgements

This thesis owes its existence to the help, guidance, and support of many people. I would like to thank all of you who have supported me throughout my research, clinical work, and personal life over the years.

First and foremost, I would like to express my deepest appreciation to my main supervisor, **Susanna Ranta**, who has provided invaluable guidance since the beginning of our collaboration. You serve as a true role model. This project would have been so much more challenging without your commitment, exceptional scientific research skills, impressive executive functioning, and extraordinary supervision. Thank you for always giving the best of support.

Co-supervisor, **Arja Harila**, deserves my sincere gratitude for your role in recruiting me for this project and constant support. I am very grateful for the opportunities you have provided me to grow as a researcher and for continuously paving the way for me to engage in exciting new research projects.

Mats Heyman, my co-supervisor, has significantly enriched my research journey with your wise counsel over the years. I feel privileged to have been introduced to the field of ALL and childhood cancer research under your co-supervision. Your guidance and valuable insights at various stages of this project are greatly appreciated.

I am also thankful for all the **co-authors**, including the national principal investigators at NOPHO, who have contributed to and critically reviewed all the papers.

Eva Hedlund, my mentor and friend. I greatly appreciate the invaluable advices and reassurance you have provided.

Pernilla Grillner, in her role as the head of the pediatric oncology department at Karolinska University Hospital, enabled and encouraged my research alongside my clinical work. Thank you for your excellent guidance, friendship, and enduring trust in me over the years.

I want to express my gratitude to **Stefan Söderhäll**, who, for whatever reasons, identified a potential in me as a pediatric oncologist early in my clinical career, hired me, and steered my path toward pediatric hematology and oncology.

Mikael Sundin, your former “mentie” wants to thank you for your clinical guidance during the residency. Our meetings were a source of encouragement, guidance, and friendship that greatly assisted in managing the balance between daily clinical work and research.

Andrea Merker, the master BMI- and growth curve expert. The future Tim Cole. Thank you for all your help and enjoyable lunches.

All of my dear **colleagues** and **staff** at the Pediatric Oncology Department at Karolinska University Hospital, it is indeed a privilege to work alongside you. I very much enjoy the clinical work, and the reason for this is each and every one of you.

I would also like to express my appreciation for my colleagues at the Division for Pediatric Oncology and Surgery at KBH, Karolinska Institutet, especially **Désirée Gavhed**, the senior research specialist, for her invaluable administrative support over the years, and **Anna Nilsson**, the head of the division, for her consistent mentoring and encouraging words in both clinical work and research.

Ida Hed Myrberg, thank you for providing excellent guidance as I ventured into the world of statistics.

Åsa Dickson, I appreciate your support during the dissertation planning. Your experience and enthusiasm have not only been invaluable but have also provided a comforting reassurance.

I extend a big thank you to the funding agency that supported this thesis: **The Swedish Childhood Cancer Fund** (Barncancerfonden).

Thank you to my **friends**, **Kristin**, **Carin**, **Anna-Marie**, **Cecilia** and **Tessa**, steadfast in sharing both my concerns and moments of joy. My dear cousin **Ann-Sofie**, I will forever cherish the visits to you in Lübeck.

My parents, **Solvej** and **Claes**, your boundless energy and fearlessness in embracing new challenges and adventures have been a constant inspiration. I am so grateful for Varglund, a haven where we can all gather. My warm gratitude also goes to my brother **Robert** and my sister-in-law, **Ditte**, for all your help and encouragement from medical school to Ph.D. My other dear siblings, **Henrik**, **Elisabeth**, and **Johan**, what would life be without you?

Lastly, I would like to thank my husband **Johan**, the one who had to take the consequences of my absorption into this project. You have been truly exceptional, consistently providing support and stability during my hectic moments of racing against deadlines or when my thoughts and energy were dedicated to my research. I am immensely grateful to have you in my life, and I thank you for making this journey possible. Our children, **Herman**, **Clara** and **Hannes**. I am so proud to be your mother.

9 References

1. Kampen KR. The discovery and early understanding of leukemia. *Leuk Res.* 2012;36(1):6-13.
2. Seibel NL. Acute lymphoblastic leukemia: an historical perspective. *Hematology Am Soc Hematol Educ Program.* 2008:365.
3. Pui CH, Yang JJ, Hunger SP, et al. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. *J Clin Oncol.* 2015;33(27):2938-2948.
4. Toft N, Birgens H, Abrahamsson J, et al. Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. *Leukemia.* 2018;32(3):606-615.
5. Winter SS, Dunsmore KP, Devidas M, et al. Improved Survival for Children and Young Adults With T-Lineage Acute Lymphoblastic Leukemia: Results From the Children's Oncology Group AALL0434 Methotrexate Randomization. *J Clin Oncol.* 2018;36(29):2926-2934.
6. Maloney KW, Devidas M, Wang C, et al. Outcome in Children With Standard-Risk B-Cell Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0331. *J Clin Oncol.* 2020;38(6):602-612.
7. Schmiegelow K, Forestier E, Hellebostad M, et al. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. *Leukemia.* 2010;24(2):345-354.
8. Moricke A, Zimmermann M, Reiter A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia.* 2010;24(2):265-284.
9. Gaynon PS, Angiolillo AL, Carroll WL, et al. Long-term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983-2002: a Children's Oncology Group Report. *Leukemia.* 2010;24(2):285-297.
10. Katz AJ, Chia VM, Schoonen WM, Kelsh MA. Acute lymphoblastic leukemia: an assessment of international incidence, survival, and disease burden. *Cancer Causes Control.* 2015;26(11):1627-1642.
11. Lim JY, Bhatia S, Robison LL, Yang JJ. Genomics of racial and ethnic disparities in childhood acute lymphoblastic leukemia. *Cancer.* 2014;120(7):955-962.
12. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72(1):7-33.
13. Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet.* 2020;395(10230):1146-1162.
14. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. *Lancet.* 2008;371(9617):1030-1043.
15. Bjork-Eriksson T, Bostrom M, Bryngelsson IL, et al. Mortality Among Pediatric Patients With Acute Lymphoblastic Leukemia in Sweden From 1988 to 2017. *JAMA Netw Open.* 2022;5(11):e2243857.
16. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol.* 1996;14(1):18-24.
17. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol.* 2012;30(14):1663-1669.
18. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J.* 2017;7(6):e577.

19. Roberts KG. Genetics and prognosis of ALL in children vs adults. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):137-145.
20. Vrooman LM, Silverman LB. Treatment of Childhood Acute Lymphoblastic Leukemia: Prognostic Factors and Clinical Advances. *Curr Hematol Malig Rep.* 2016;11(5):385-394.
21. Rubnitz JE, Lensing S, Zhou Y, et al. Death during induction therapy and first remission of acute leukemia in childhood: the St. Jude experience. *Cancer.* 2004;101(7):1677-1684.
22. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. *Haematologica.* 2020;105(11):2524-2539.
23. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. *New England Journal of Medicine.* 2015;373(16):1541-1552.
24. Teachey DT, Pui CH. Comparative features and outcomes between paediatric T-cell and B-cell acute lymphoblastic leukaemia. *Lancet Oncol.* 2019;20(3):e142-e154.
25. Brown P, Inaba H, Annesley C, et al. Pediatric Acute Lymphoblastic Leukemia, Version 2.2020. *Journal of the National Comprehensive Cancer Network.* 2020;18(1):81-112.
26. Moorman AV. New and emerging prognostic and predictive genetic biomarkers in B-cell precursor acute lymphoblastic leukemia. *Haematologica.* 2016;101(4):407-416.
27. Berry DA, Zhou S, Higley H, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. *JAMA Oncol.* 2017;3(7):e170580.
28. Oskarsson T, Soderhall S, Arvidson J, et al. Relapsed childhood acute lymphoblastic leukemia in the Nordic countries: prognostic factors, treatment and outcome. *Haematologica.* 2016;101(1):68-76.
29. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. *N Engl J Med.* 2015;373(16):1541-1552.
30. Stanulla M, Cavé H, Moorman AV. IKZF1 deletions in pediatric acute lymphoblastic leukemia: still a poor prognostic marker? *Blood.* 2020;135(4):252-260.
31. Raja RA, Schmiegelow K, Albertsen BK, et al. Asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol. *Br J Haematol.* 2014;165(1):126-133.
32. Toft N, Birgens H, Abrahamsson J, et al. Risk group assignment differs for children and adults 1-45 yr with acute lymphoblastic leukemia treated by the NOPHO ALL-2008 protocol. *Eur J Haematol.* 2013;90(5):404-412.
33. Toft N, Birgens H, Abrahamsson J, et al. Toxicity profile and treatment delays in NOPHO ALL2008-comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Eur J Haematol.* 2016;96(2):160-169.
34. Egnell C, Heyman M, Jonsson OG, et al. Obesity as a predictor of treatment-related toxicity in children with acute lymphoblastic leukaemia. *Br J Haematol.* 2022;196(5):1239-1247.
35. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. *Lancet Oncol.* 2013;14(3):199-209.
36. Angiolillo AL, Schore RJ, Kairalla JA, et al. Excellent Outcomes With Reduced Frequency of Vincristine and Dexamethasone Pulses in Standard-Risk B-Lymphoblastic Leukemia: Results From Children's Oncology Group AALL0932. *J Clin Oncol.* 2021;39(13):1437-1447.

37. Bhojwani D, Pui CH. Relapsed childhood acute lymphoblastic leukaemia. *Lancet Oncol.* 2013;14(6):e205-217.
38. Lobstein T. Obesity prevention and the Global Syndemic: Challenges and opportunities for the World Obesity Federation. *Obes Rev.* 2019;20 Suppl 2:6-9.
39. Spinelli A, Buoncristiano M, Kovacs VA, et al. Prevalence of Severe Obesity among Primary School Children in 21 European Countries. *Obes Facts.* 2019;12(2):244-258.
40. Miregard J, Nowicka P, Nylander C. National data showed an increased prevalence of overweight and obesity among four-year-old Swedish children during the first year of COVID-19. *Acta Paediatr.* 2023;112(6):1269-1274.
41. Horesh A, Tsur AM, Bardugo A, Twig G. Adolescent and Childhood Obesity and Excess Morbidity and Mortality in Young Adulthood-a Systematic Review. *Curr Obes Rep.* 2021;10(3):301-310.
42. Jebeile H, Cardel MI, Kyle TK, Jastreboff AM. Addressing psychosocial health in the treatment and care of adolescents with obesity. *Obesity (Silver Spring).* 2021;29(9):1413-1422.
43. Vogel M, Geserick M, Gausche R, et al. Age- and weight group-specific weight gain patterns in children and adolescents during the 15 years before and during the COVID-19 pandemic. *Int J Obes (Lond).* 2022;46(1):144-152.
44. Woolford SJ, Sidell M, Li X, et al. Changes in Body Mass Index Among Children and Adolescents During the COVID-19 Pandemic. *JAMA.* 2021;326(14):1434-1436.
45. Baillargeon J, Langevin AM, Lewis M, et al. Therapy-related changes in body size in Hispanic children with acute lymphoblastic leukemia. *Cancer.* 2005;103(8):1725-1729.
46. Orgel E, Mueske NM, Sposto R, Gilsanz V, Freyer DR, Mittelman SD. Limitations of body mass index to assess body composition due to sarcopenic obesity during leukemia therapy. *Leuk Lymphoma.* 2018;59(1):138-145.
47. Kuczmarski RJ. *2000 CDC growth charts for the United States: methods and development.* Department of Health and Human Services, Centers for Disease Control and …; 2002.
48. de Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? *Int J Pediatr Obes.* 2010;5(6):458-460.
49. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ.* 2007;85(9):660-667.
50. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ.* 2000;320(7244):1240-1243.
51. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ.* 2007;335(7612):194.
52. Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr.* 1990;44(1):45-60.
53. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes.* 2012;7(4):284-294.
54. Pietrobelli A, Faith MS, Allison DB, Gallagher D, Chiumello G, Heymsfield SB. Body mass index as a measure of adiposity among children and adolescents: a validation study. *J Pediatr.* 1998;132(2):204-210.
55. Hijiya N, Panetta JC, Zhou Y, et al. Body mass index does not influence pharmacokinetics or outcome of treatment in children with acute lymphoblastic leukemia. *Blood.* 2006;108(13):3997-4002.

56. Aldhafiri FK, McColl JH, Reilly JJ. Prognostic significance of being overweight and obese at diagnosis in children with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol.* 2014;36(3):234-236.
57. Eissa HM, Zhou Y, Panetta JC, et al. The effect of body mass index at diagnosis on clinical outcome in children with newly diagnosed acute lymphoblastic leukemia. *Blood Cancer J.* 2017;7(2):e531.
58. Ethier MC, Alexander S, Abla O, Green G, Lam R, Sung L. Association between obesity at diagnosis and weight change during induction and survival in pediatric acute lymphoblastic leukemia. *Leuk Lymphoma.* 2012;53(9):1677-1681.
59. Orgel E, Sposto R, Malvar J, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: A report from the Children's Oncology Group. *J Clin Oncol.* 2014;32(13):1331-1337.
60. Orgel E, Tucci J, Alhushki W, et al. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. *Blood.* 2014;124(26):3932-3938.
61. Butturini AM, Dorey FJ, Lange BJ, et al. Obesity and outcome in pediatric acute lymphoblastic leukemia. *J Clin Oncol.* 2007;25(15):2063-2069.
62. Rolland-Cachera MF. Childhood obesity: current definitions and recommendations for their use. *Int J Pediatr Obes.* 2011;6(5-6):325-331.
63. Group WHOMGRS. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl.* 2006;450:76-85.
64. Collaborators GBDO, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med.* 2017;377(1):13-27.
65. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet.* 2017;390(10113):2627-2642.
66. Larsson SC, Wolk A. Overweight and obesity and incidence of leukemia: a meta-analysis of cohort studies. *Int J Cancer.* 2008;122(6):1418-1421.
67. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. *J Obes.* 2013;2013:291546.
68. Ghosh T, Richardson M, Gordon PM, Ryder JR, Spector LG, Turcotte LM. Body mass index associated with childhood and adolescent high-risk B-cell acute lymphoblastic leukemia risk: A Children's Oncology Group report. *Cancer Med.* 2020;9(18):6825-6835.
69. Marley AR, Domingues A, Ghosh T, Turcotte LM, Spector LG. Maternal Body Mass Index, Diabetes, and Gestational Weight Gain and Risk for Pediatric Cancer in Offspring: A Systematic Review and Meta-Analysis. *JNCI Cancer Spectr.* 2022;6(2).
70. Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. *Int J Cancer.* 2009;124(11):2658-2670.
71. Amankwah EK, Saenz AM, Hale GA, Brown PA. Association between body mass index at diagnosis and pediatric leukemia mortality and relapse: a systematic review and meta-analysis. *Leuk Lymphoma.* 2016;57(5):1140-1148.
72. Orgel E, Genkinger JM, Aggarwal D, Sung L, Nieder M, Ladas EJ. Association of body mass index and survival in pediatric leukemia: a meta-analysis. *Am J Clin Nutr.* 2016;103(3):808-817.
73. Paviglianiti A. A Review on the Impact of Body Mass Index on Outcomes in Pediatric Leukemia. *J Blood Med.* 2020;11:205-212.

74. Saenz AM, Stapleton S, Hernandez RG, et al. Body Mass Index at Pediatric Leukemia Diagnosis and the Risks of Relapse and Mortality: Findings from a Single Institution and Meta-analysis. *J Obes.* 2018;2018:7048078.
75. Baillargeon J, Langevin AM, Lewis M, et al. Obesity and survival in a cohort of predominantly Hispanic children with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol.* 2006;28(9):575-578.
76. Galati PC, Rocha PRS, Gruezo ND, Amato AA. Body mass trajectory from diagnosis to the end of treatment in a pediatric acute lymphoblastic leukemia cohort. *Sci Rep.* 2023;13(1):13590.
77. Barr RD. Nutritional status in children with cancer: Before, during and after therapy. *Indian J Cancer.* 2015;52(2):173-175.
78. Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition--A dynamic triangle in review. *Cancer.* 2004;100(4):677-687.
79. Triarico S, Rinninella E, Cintoni M, et al. Impact of malnutrition on survival and infections among pediatric patients with cancer: a retrospective study. *Eur Rev Med Pharmacol Sci.* 2019;23(3):1165-1175.
80. den Hoed MA, Pluijm SM, de Groot-Kruseman HA, et al. The negative impact of being underweight and weight loss on survival of children with acute lymphoblastic leukemia. *Haematologica.* 2015;100(1):62-69.
81. Barr RD, Mosby TT. Nutritional status in children and adolescents with leukemia: An emphasis on clinical outcomes in low and middle income countries. *Hematology.* 2016;21(4):199-205.
82. Caniza MA, Odio C, Mukkada S, et al. Infectious complications in children with acute lymphoblastic leukemia treated in low-middle-income countries. *Expert Rev Hematol.* 2015;8(5):627-645.
83. Martin-Trejo JA, Nunez-Enriquez JC, Fajardo-Gutierrez A, et al. Early mortality in children with acute lymphoblastic leukemia in a developing country: the role of malnutrition at diagnosis. A multicenter cohort MIGICCL study. *Leuk Lymphoma.* 2017;58(4):898-908.
84. Nunez-Enriquez JC, Gil-Hernandez AE, Jimenez-Hernandez E, et al. Overweight and obesity as predictors of early mortality in Mexican children with acute lymphoblastic leukemia: a multicenter cohort study. *BMC Cancer.* 2019;19(1):708.
85. Hu W, Cheung YT, Tang Y, et al. Association between body mass index at diagnosis and outcomes in Chinese children with newly diagnosed acute lymphoblastic leukemia. *Cancer Med.* 2023;12(3):2850-2860.
86. Smith DE, Stevens MC, Booth IW. Malnutrition at diagnosis of malignancy in childhood: common but mostly missed. *Eur J Pediatr.* 1991;150(5):318-322.
87. Fernandez CV, Anderson J, Breslow NE, et al. Anthropomorphic measurements and event-free survival in patients with favorable histology Wilms tumor: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2009;52(2):254-258.
88. Joffe L, Dwyer S, Glade Bender JL, Frazier AL, Ladas EJ. Nutritional status and clinical outcomes in pediatric patients with solid tumors : A systematic review of the literature. *Semin Oncol.* 2019;46(1):48-56.
89. Lashinger LM, Rossi EL, Hursting SD. Obesity and resistance to cancer chemotherapy: interacting roles of inflammation and metabolic dysregulation. *Clin Pharmacol Ther.* 2014;96(4):458-463.
90. Haslam D. Obesity: a medical history. *Obes Rev.* 2007;8 Suppl 1:31-36.
91. Orgel E, Mittelman SD. The links between insulin resistance, diabetes, and cancer. *Curr Diab Rep.* 2013;13(2):213-222.

92. Orgel E, Sea JL, Mittelman SD. Mechanisms by Which Obesity Impacts Survival from Acute Lymphoblastic Leukemia. *J Natl Cancer Inst Monogr.* 2019;2019(54):152-156.
93. Brill MJ, Diepstraten J, van Rongen A, van Kralingen S, van den Anker JN, Knibbe CA. Impact of obesity on drug metabolism and elimination in adults and children. *Clin Pharmacokinet.* 2012;51(5):277-304.
94. Lan N, Lu Y, Zhang Y, et al. FTO - A Common Genetic Basis for Obesity and Cancer. *Front Genet.* 2020;11:559138.
95. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflamm.* 2013;2013:139239.
96. Zinngrebe J, Debatin KM, Fischer-Posovszky P. Adipocytes in hematopoiesis and acute leukemia: friends, enemies, or innocent bystanders? *Leukemia.* 2020;34(9):2305-2316.
97. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003;112(12):1796-1808.
98. Ambrosi TH, Scialdone A, Graja A, et al. Adipocyte Accumulation in the Bone Marrow during Obesity and Aging Impairs Stem Cell-Based Hematopoietic and Bone Regeneration. *Cell Stem Cell.* 2017;20(6):771-784 e776.
99. Behan JW, Yun JP, Proektor MP, et al. Adipocytes impair leukemia treatment in mice. *Cancer Res.* 2009;69(19):7867-7874.
100. Pramanik R, Sheng X, Ichihara B, Heisterkamp N, Mittelman SD. Adipose tissue attracts and protects acute lymphoblastic leukemia cells from chemotherapy. *Leuk Res.* 2013;37(5):503-509.
101. Ehsanipour EA, Sheng X, Behan JW, et al. Adipocytes cause leukemia cell resistance to L-asparaginase via release of glutamine. *Cancer Res.* 2013;73(10):2998-3006.
102. Tucci J, Chen T, Margulis K, et al. Adipocytes Provide Fatty Acids to Acute Lymphoblastic Leukemia Cells. *Front Oncol.* 2021;11:665763.
103. Harskamp-van Ginkel MW, Hill KD, Becker KC, et al. Drug Dosing and Pharmacokinetics in Children With Obesity: A Systematic Review. *JAMA Pediatr.* 2015;169(7):678-685.
104. Kendrick JG, Carr RR, Ensom MH. Pharmacokinetics and drug dosing in obese children. *J Pediatr Pharmacol Ther.* 2010;15(2):94-109.
105. Gerhart JG, Balevic S, Sinha J, et al. Characterizing Pharmacokinetics in Children With Obesity-Physiological, Drug, Patient, and Methodological Considerations. *Front Pharmacol.* 2022;13:818726.
106. Toft N, Birgens H, Abrahamsson J, et al. Toxicity profile and treatment delays in NOPHO ALL2008-comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Eur J Haematol.* 2016;96(2):160-169.
107. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. *Clin Pharmacokinet.* 2000;39(3):215-231.
108. Hall RG, 2nd, Jean GW, Sigler M, Shah S. Dosing considerations for obese patients receiving cancer chemotherapeutic agents. *Ann Pharmacother.* 2013;47(12):1666-1674.
109. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet.* 2010;49(2):71-87.
110. Kotlyar M, Carson SW. Effects of obesity on the cytochrome P450 enzyme system. *Int J Clin Pharmacol Ther.* 1999;37(1):8-19.

111. Fancher KM, Sacco AJ, Gwin RC, Gormley LK, Mitchell CB. Comparison of two different formulas for body surface area in adults at extremes of height and weight. *Journal of Oncology Pharmacy Practice.* 2016;22(5):690-695.
112. Mulla H, Johnson TN. Dosing dilemmas in obese children. *Arch Dis Child Educ Pract Ed.* 2010;95(4):112-117.
113. Ellis KJ. Human body composition: in vivo methods. *Physiol Rev.* 2000;80(2):649-680.
114. Duarte X, Esteves S, Neto AM, Pereira F. Incidence and risk factors for Central Nervous System thrombosis in paediatric acute lymphoblastic leukaemia during intensive asparaginase treatment: a single-centre cohort study. *Br J Haematol.* 2016;174(2):280-291.
115. Niinimaki RA, Harila-Saari AH, Jartti AE, et al. High body mass index increases the risk for osteonecrosis in children with acute lymphoblastic leukemia. *J Clin Oncol.* 2007;25(12):1498-1504.
116. Lowas S, Malempati S, Marks D. Body mass index predicts insulin resistance in survivors of pediatric acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2009;53(1):58-63.
117. Sonabend RY, McKay SV, Okcu MF, Yan J, Haymond MW, Margolin JF. Hyperglycemia during induction therapy is associated with poorer survival in children with acute lymphocytic leukemia. *J Pediatr.* 2009;155(1):73-78.
118. Trelinska J, Fendler W, Szadkowska A, et al. Hypoglycemia and glycemic variability among children with acute lymphoblastic leukemia during maintenance therapy. *Leuk Lymphoma.* 2011;52(9):1704-1710.
119. Brennan RC, Helton KJ, Pei D, et al. Spinal epidural lipomatosis in children with hematologic malignancies. *Ann Hematol.* 2011;90(9):1067-1074.
120. Mogensen PR, Wolthers BO, Grell K, Schmiegelow K, Frandsen TL. Association between body mass index and pancreatitis in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2018;65(8):e27071.
121. Browne EK, Zhou Y, Chemaitilly W, et al. Changes in body mass index, height, and weight in children during and after therapy for acute lymphoblastic leukemia. *Cancer.* 2018;124(21):4248-4259.
122. Withycombe JS, Smith LM, Meza JL, et al. Weight change during childhood acute lymphoblastic leukemia induction therapy predicts obesity: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2015;62(3):434-439.
123. Zhang FF, Rodday AM, Kelly MJ, et al. Predictors of being overweight or obese in survivors of pediatric acute lymphoblastic leukemia (ALL). *Pediatr Blood Cancer.* 2014;61(7):1263-1269.
124. Belle FN, Wenke-Zobler J, Cignacco E, et al. Overweight in childhood cancer patients at diagnosis and throughout therapy: A multicentre cohort study. *Clin Nutr.* 2019;38(2):835-841.
125. Foster KL, Kern KD, Chambers TM, et al. Weight trends in a multiethnic cohort of pediatric acute lymphoblastic leukemia survivors: A longitudinal analysis. *PLoS One.* 2019;14(5):e0217932.
126. Arpe ML, Rorvig S, Kok K, Molgaard C, Frandsen TL. The association between glucocorticoid therapy and BMI z-score changes in children with acute lymphoblastic leukemia. *Support Care Cancer.* 2015;23(12):3573-3580.
127. Barbosa JM, Diniz Araujo ML, Lins MM, et al. Excess Weight among Survivors of Acute Lymphoblastic Leukemia Survivors Treated at a Center in Northeast Brazil. *Nutr Cancer.* 2022;74(9):3292-3301.

128. Ahmed SF, Tucker P, Mushtaq T, Wallace AM, Williams DM, Hughes IA. Short-term effects on linear growth and bone turnover in children randomized to receive prednisolone or dexamethasone. *Clin Endocrinol (Oxf).* 2002;57(2):185-191.
129. Wallace AM, Tucker P, Williams DM, Hughes IA, Ahmed SF. Short-term effects of prednisolone and dexamethasone on circulating concentrations of leptin and sex hormone-binding globulin in children being treated for acute lymphoblastic leukaemia. *Clin Endocrinol (Oxf).* 2003;58(6):770-776.
130. Rogers PC, Meacham LR, Oeffinger KC, Henry DW, Lange BJ. Obesity in pediatric oncology. *Pediatr Blood Cancer.* 2005;45(7):881-891.
131. Atkinson HC, Marsh JA, Rath SR, et al. Increased Body Mass Index during Therapy for Childhood Acute Lymphoblastic Leukemia: A Significant and Underestimated Complication. *Int J Pediatr.* 2015;2015:386413.
132. Gustaite S, Everatt V, Kairiene I, Vaisnore R, Rascon J, Vaitkeviciene GE. Changes in Nutritional Status during Induction Phase and Their Association with Fever and Minimal Residual Disease in Paediatric Acute Lymphoblastic Leukaemia. *Medicina (Kaunas).* 2023;59(6).
133. Orgel E, Framson C, Buxton R, et al. Caloric and nutrient restriction to augment chemotherapy efficacy for acute lymphoblastic leukemia: the IDEAL trial. *Blood Adv.* 2021;5(7):1853-1861.
134. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet.* 2017;390(10112):2569-2582.
135. Pluimakers VG, van Waas M, Neggers S, van den Heuvel-Eibrink MM. Metabolic syndrome as cardiovascular risk factor in childhood cancer survivors. *Crit Rev Oncol Hematol.* 2019;133:129-141.
136. Ehrhardt MJ, Liu Q, Dixon SB, et al. Association of Modifiable Health Conditions and Social Determinants of Health With Late Mortality in Survivors of Childhood Cancer. *JAMA Netw Open.* 2023;6(2):e2255395.
137. Kartal I, Alacam A, Dagdemir A, et al. Frequency of obesity and metabolic syndrome in childhood leukemia and lymphoma survivors. *Diabetol Metab Syndr.* 2022;14(1):16.
138. Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in pediatric ALL survivors: a meta-analysis. *Pediatrics.* 2014;133(3):e704-715.
139. Rayar M, Webber CE, Nayiager T, Sala A, Barr RD. Sarcopenia in children with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol.* 2013;35(2):98-102.
140. Orgel E, Mueske NM, Wren TA, et al. Early injury to cortical and cancellous bone from induction chemotherapy for adolescents and young adults treated for acute lymphoblastic leukemia. *Bone.* 2016;85:131-137.
141. Marriott CJC, Beaumont LF, Farncombe TH, et al. Body composition in long-term survivors of acute lymphoblastic leukemia diagnosed in childhood and adolescence: A focus on sarcopenic obesity. *Cancer.* 2018;124(6):1225-1231.
142. Brinksma A, Sulkers E, Kouwenberg D, et al. Changes in body size and body composition in survivors of childhood cancer: seven years follow-up of a prospective cohort study. *Clin Nutr.* 2022;41(12):2778-2785.
143. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer. *J Clin Oncol.* 2018;36(21):2181-2189.

144. Iijima M, Liu W, Panetta JC, et al. Association between obesity and neurocognitive function in survivors of childhood acute lymphoblastic leukemia treated only with chemotherapy. *Cancer.* 2021;127(17):3202-3213.
145. Kato M, Manabe A. Treatment and biology of pediatric acute lymphoblastic leukemia. *Pediatr Int.* 2018;60(1):4-12.
146. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. *Oncologist.* 2016;21(12):1471-1482.
147. Schmidt D, Kristensen K, Schroeder H, et al. Plasma creatinine as predictor of delayed elimination of high-dose methotrexate in childhood acute lymphoblastic leukemia: A Danish population-based study. *Pediatric blood & cancer.* 2019:e27637.
148. Treviño LR, Shimasaki N, Yang W, et al. Germline genetic variation in an organic anion transporter polypeptide associated with methotrexate pharmacokinetics and clinical effects. *Journal of Clinical Oncology.* 2009;27(35):5972-5978.
149. Gregers J, Christensen IJ, Dalhoff K, et al. The association of reduced folate carrier 80G> A polymorphism to outcome in childhood acute lymphoblastic leukemia interacts with chromosome 21 copy number. *Blood.* 2010;115(23):4671-4677.
150. Mikkelsen TS, Thorn CF, Yang JJ, et al. PharmGKB summary: methotrexate pathway. *Pharmacogenetics and genomics.* 2011;21(10):679.
151. Ramsey LB, Bruun GH, Yang W, et al. Rare versus common variants in pharmacogenetics: SLCO1B1 variation and methotrexate disposition. *Genome research.* 2012;22(1):1-8.
152. Christensen AM, Pauley JL, Molinelli AR, et al. Resumption of high-dose methotrexate after acute kidney injury and glucarpidase use in pediatric oncology patients. *Cancer.* 2012;118(17):4321-4330.
153. Svahn T, Mellgren K, Harila-Saari A, et al. Delayed elimination of high-dose methotrexate and use of carboxypeptidase G2 in pediatric patients during treatment for acute lymphoblastic leukemia. *Pediatric blood & cancer.* 2017;64(7).
154. Mikkelsen TS, Sparreboom A, Cheng C, et al. Shortening infusion time for high-dose methotrexate alters antileukemic effects: a randomized prospective clinical trial. *Journal of clinical oncology.* 2011;29(13):1771-1778.
155. Relling MV, Fairclough D, Ayers D, et al. Patient characteristics associated with high-risk methotrexate concentrations and toxicity. *Journal of Clinical Oncology.* 1994;12(8):1667-1672.
156. Sterba J, Dusek L, Demlova R, Valik D. Pretreatment plasma folate modulates the pharmacodynamic effect of high-dose methotrexate in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma: "folate overrescue" concept revisited. *Clin Chem.* 2006;52(4):692-700.
157. Skarby TV, Anderson H, Heldrup J, et al. High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. *Leukemia.* 2006;20(11):1955-1962.
158. Orgel E, Nabais T, Douglas C, Mittelman SD, Neely M. Effect of Body Fat on Population Pharmacokinetics of High-Dose Methotrexate in Pediatric Patients With Acute Lymphoblastic Leukemia. *J Clin Pharmacol.* 2021;61(6):755-762.
159. Gallais F, Oberic L, Faguer S, et al. Body Surface Area Dosing of High-Dose Methotrexate Should Be Reconsidered, Particularly in Overweight, Adult Patients. *Ther Drug Monit.* 2021;43(3):408-415.
160. Mandal P, Samaddar S, Chandra J, Parakh N, Goel M. Adverse effects with intravenous methotrexate in children with acute lymphoblastic

leukemia/lymphoma: a retrospective study. *Indian J Hematol Blood Transfus.* 2020;36(3):498-504.
161. Jain H, Rajendra A, Sengar M, et al. The current treatment approach to adolescents and young adults with acute lymphoblastic leukemia (AYA-ALL): challenges and considerations. *Expert Rev Anticancer Ther.* 2022;22(8):845-860.
162. Neaga A, Jimbu L, Mesaros O, et al. Why Do Children with Acute Lymphoblastic Leukemia Fare Better Than Adults? *Cancers (Basel).* 2021;13(15).
163. Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol.* 2009;27(6):911-918.
164. DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia.* 2015;29(3):526-534.
165. Ram R, Wolach O, Vidal L, Gafter-Gvili A, Shpilberg O, Raanani P. Adolescents and young adults with acute lymphoblastic leukemia have a better outcome when treated with pediatric-inspired regimens: systematic review and meta-analysis. *Am J Hematol.* 2012;87(5):472-478.
166. Advani AS, Larsen E, Laumann K, et al. Comparison of CALGB 10403 (Alliance) and COG AALL0232 toxicity results in young adults with acute lymphoblastic leukemia. *Blood Adv.* 2021;5(2):504-512.
167. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood.* 2019;133(14):1548-1559.
168. Shimony S, Flamand Y, Valtis YK, et al. Effect of BMI on toxicities and survival among adolescents and young adults treated on DFCI Consortium ALL trials. *Blood Adv.* 2023;7(18):5234-5245.
169. Heiblig M, Elhamri M, Nicolini FE, et al. Effect of Initial Body Mass Index on Survival Outcome of Patients With Acute Leukemia: A Single-Center Retrospective Study. *Clin Lymphoma Myeloma Leuk.* 2015;15 Suppl:S7-13.
170. Aleixo GFP, Sheu M, Mirzai S, Majhail NS. Prognostic Impact of Adiposity in Hematological Malignancies: A Systematic Review and Meta-analysis. *Clin Lymphoma Myeloma Leuk.* 2022;22(10):726-734.
171. Purnell JQ. Definitions, Classification, and Epidemiology of Obesity. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext.* South Dartmouth (MA)2000.
172. Egnell C, Ranta S, Banerjee J, et al. Impact of body mass index on relapse in children with acute lymphoblastic leukemia treated according to Nordic treatment protocols. *Eur J Haematol.* 2020;105(6):797-807.
173. van Gameren-Oosterom HB, van Dommelen P, Schonbeck Y, Oudesluys-Murphy AM, van Wouwe JP, Buitendijk SE. Prevalence of overweight in Dutch children with Down syndrome. *Pediatrics.* 2012;130(6):e1520-1526.
174. Buitenkamp TD, Izraeli S, Zimmermann M, et al. Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. *Blood.* 2014;123(1):70-77.
175. Egnell C, Narhinen H, Merker A, et al. Changes in body mass index during treatment of childhood acute lymphoblastic leukemia with the Nordic ALL2008 protocol. *Eur J Haematol.* 2022;109(6):656-663.
176. Chen AR, Wang YM, Lin M, Kuo DJ. High-Dose Methotrexate in Pediatric Acute Lymphoblastic Leukemia: Predictors of Delayed Clearance and the Effect of Increased Hydration Rate on Methotrexate Clearance. *Cureus.* 2020;12(6):e8674.

177. Schmidt D, Kristensen K, Schroeder H, et al. Plasma creatinine as predictor of delayed elimination of high-dose methotrexate in childhood acute lymphoblastic leukemia: A Danish population-based study. *Pediatr Blood Cancer.* 2019;66(6):e27637.
178. Sun J, Zhang R, Tang J, et al. Prognostic Observational Analysis of BMI, Leptin, and Adiponectin in Children With Acute Lymphocytic Leukemia Undergoing Remission-Induction Chemotherapy. *Front Pediatr.* 2022;10:797836.
179. Tripodi SI, Bergami E, Panigari A, et al. The role of nutrition in children with cancer. *Tumori.* 2023;109(1):19-27.
180. Denton CC, Rawlins YA, Oberley MJ, Bhojwani D, Orgel E. Predictors of hepatotoxicity and pancreatitis in children and adolescents with acute lymphoblastic leukemia treated according to contemporary regimens. *Pediatr Blood Cancer.* 2018;65(3).
181. Christ TN, Stock W, Knoebel RW. Incidence of asparaginase-related hepatotoxicity, pancreatitis, and thrombotic events in adults with acute lymphoblastic leukemia treated with a pediatric-inspired regimen. *J Oncol Pharm Pract.* 2018;24(4):299-308.
182. Silva WFD, Massaut IHB, Bendlin RM, et al. Toxicity Profile of PEG-Asparaginase in Adult Patients With Acute Lymphoblastic Leukemia in Brazil: A Multicenter Cross-Sectional Study. *Clin Lymphoma Myeloma Leuk.* 2020;20(8):e523-e528.
183. Hashmi SK, Navai SA, Chambers TM, et al. Incidence and predictors of treatment-related conjugated hyperbilirubinemia during early treatment phases for children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2020;67(2):e28063.
184. Roberson JR, Spraker HL, Shelso J, et al. Clinical consequences of hyperglycemia during remission induction therapy for pediatric acute lymphoblastic leukemia. *Leukemia.* 2009;23(2):245-250.
185. Pollock NI, Flamand Y, Zhu J, et al. Hyperglycemia during induction therapy for acute lymphoblastic leukemia is temporally linked to pegaspargase administration. *Pediatr Blood Cancer.* 2022;69(7):e29505.
186. Tosur M, Viau-Colindres J, Astudillo M, Redondo MJ, Lyons SK. Medication-induced hyperglycemia: pediatric perspective. *BMJ Open Diabetes Res Care.* 2020;8(1).
187. Demedis J, Scarbro S, Suresh K, Maloney K, Forlenza GP. Hyperglycemia and Other Glycemic Measures Throughout Therapy for Pediatric Acute Lymphoblastic Leukemia and Lymphoma. *J Pediatr Hematol Oncol.* 2023;45(2):e154-e160.
188. Meenan CK, Kelly JA, Wang L, Ritchey AK, Maurer SH. Obesity in pediatric patients with acute lymphoblastic leukemia increases the risk of adverse events during pre-maintenance chemotherapy. *Pediatr Blood Cancer.* 2019;66(2):e27515.
189. Hingorani P, Seidel K, Krailo M, et al. Body mass index (BMI) at diagnosis is associated with surgical wound complications in patients with localized osteosarcoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2011;57(6):939-942.
190. Lange BJ, Gerbing RB, Feusner J, et al. Mortality in Overweight and Underweight Children With Acute Myeloid Leukemia. *JAMA.* 2005;293(2):203-211.
191. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood.* 2001;97(5):1211-1218.
192. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *Journal of clinical oncology.* 2013;31(9):1202-1210.

193. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood.* 2007;109(3):896-904.
194. Gottschalk Højfeldt S, Grell K, Abrahamsson J, et al. Relapse risk following truncation of PEG-asparaginase in childhood acute lymphoblastic leukemia. *Blood.* 2020.
195. Ishida H, Imamura T, Tatebe Y, et al. Impact of asparaginase discontinuation on outcomes of children with acute lymphoblastic leukaemia receiving the Japan Association of Childhood Leukaemia Study ALL-02 protocol. *Br J Haematol.* 2023;201(6):1200-1208.
196. Bruzzi P, Predieri B, Corrias A, et al. Final height and body mass index in adult survivors of childhood acute lymphoblastic leukemia treated without cranial radiotherapy: a retrospective longitudinal multicenter Italian study. *BMC Pediatr.* 2014;14:236.
197. Wadhwa A, Chen Y, Hageman L, et al. Body mass index during maintenance therapy and relapse risk in children with acute lymphoblastic leukemia: A Children's Oncology Group report. *Cancer.* 2023;129(1):151-160.
198. Kagawa Y, Mukohara R, Hori H, Kawasaki H, Komada Y, Kojima M. Fever as a risk factor causing delayed elimination of methotrexate in pediatric patients receiving high doses of cancer chemotherapy. *Cancer Chemother Pharmacol.* 2004;54(1):34-38.
199. Yang L, Panetta JC, Cai X, et al. Asparaginase may influence dexamethasone pharmacokinetics in acute lymphoblastic leukemia. *J Clin Oncol.* 2008;26(12):1932-1939.
200. Ramsey LB, Panetta JC, Smith C, et al. Genome-wide study of methotrexate clearance replicates SLCO1B1. *Blood.* 2013;121(6):898-904.
201. Pinhas-Hamiel O, Doron-Panush N, Reichman B, Nitzan-Kaluski D, Shalitin S, Geva-Lerner L. Obese children and adolescents: a risk group for low vitamin B12 concentration. *Arch Pediatr Adolesc Med.* 2006;160(9):933-936.
202. Sun Y, Sun M, Liu B, et al. Inverse Association Between Serum Vitamin B12 Concentration and Obesity Among Adults in the United States. *Front Endocrinol (Lausanne).* 2019;10:414.
203. Zobeck M, Bernhardt MB, Kamdar KY, Rabin KR, Lupo PJ, Scheurer ME. Novel and replicated clinical and genetic risk factors for toxicity from high-dose methotrexate in pediatric acute lymphoblastic leukemia. *Pharmacotherapy.* 2023;43(3):205-214.
204. Khera S, Sharma G, Negi V, Shaw SC. Hypoalbuminemia and not undernutrition predicts high-dose methotrexate-induced nephrotoxicity in children with acute lymphoblastic leukemia in resource-constrained centers. *Pediatr Blood Cancer.* 2022;69(9):e29738.
205. Jones SR, Patel RB, Rahim MQ, Althouse SK, Batra S. Venous Thromboembolic Events in Adolescent and Young Adult Patients with Acute Lymphoblastic Leukemia. *J Adolesc Young Adult Oncol.* 2022;11(6):600-604.
206. Wieduwilt MJ, Stock W, Advani A, et al. Superior survival with pediatric-style chemotherapy compared to myeloablative allogeneic hematopoietic cell transplantation in older adolescents and young adults with Ph-negative acute lymphoblastic leukemia in first complete remission: analysis from CALGB 10403 and the CIBMTR. *Leukemia.* 2021;35(7):2076-2085.
207. Ren G, Cai W, Wang L, et al. Impact of body mass index at different transplantation stages on postoperative outcomes in patients with hematological malignancies: a meta-analysis. *Bone Marrow Transplant.* 2018;53(6):708-721.

208. Yang J, Xue SL, Zhang X, et al. Effect of body mass index on overall survival of patients with allogeneic hematopoietic stem cell transplantation. *Eur J Clin Nutr.* 2017;71(6):750-754.
209. Barragan FA, Mills LJ, Raduski AR, et al. Genetic ancestry, differential gene expression, and survival in pediatric B-cell acute lymphoblastic leukemia. *Cancer Med.* 2023;12(4):4761-4772.
210. Gupta S, Dai Y, Chen Z, et al. Racial and ethnic disparities in childhood and young adult acute lymphocytic leukaemia: secondary analyses of eight Children's Oncology Group cohort trials. *Lancet Haematol.* 2023;10(2):e129-e141.
211. Bona K, Blonquist TM, Neuberg DS, Silverman LB, Wolfe J. Impact of Socioeconomic Status on Timing of Relapse and Overall Survival for Children Treated on Dana-Farber Cancer Institute ALL Consortium Protocols (2000–2010). *Pediatric Blood & Cancer.* 2016;63(6):1012-1018.
212. Borsi JD, Wesenberg F, Stokland T, Moe PJ. How much is too much? Folinic acid rescue dose in children with acute lymphoblastic leukaemia. *Eur J Cancer.* 1991;27(8):1006-1009.
213. Rogers PC, Ladas EJ. The impact of nutritional status on outcomes: a neglected area of research. *Pediatr Blood Cancer.* 2011;57(6):902-903.
214. Faruqi AJ, Ligon JA, Borgman P, et al. The impact of race, ethnicity, and obesity on CAR T-cell therapy outcomes. *Blood Adv.* 2022;6(23):6040-6050.
215. Hunter RJ, Navo MA, Thaker PH, Bodurka DC, Wolf JK, Smith JA. Dosing chemotherapy in obese patients: actual versus assigned body surface area (BSA). *Cancer Treat Rev.* 2009;35(1):69-78.
216. Lönnerholm G, Frost BM, Abrahamsson J, et al. Vincristine pharmacokinetics is related to clinical outcome in children with standard risk acute lymphoblastic leukemia. *Br J Haematol.* 2008;142(4):616-621.
217. Griggs JJ, Bohlke K, Balaban EP, et al. Appropriate Systemic Therapy Dosing for Obese Adult Patients With Cancer: ASCO Guideline Update. *J Clin Oncol.* 2021;39(18):2037-2048.
218. Mittelman SD, Kim J, Raca G, Li G, Oberley MJ, Orgel E. Increased prevalence of CRLF2 rearrangements in obesity-associated acute lymphoblastic leukemia. *Blood.* 2021;138(2):199-202.
219. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Battaglini CL, Williams GR. Bioelectrical Impedance Analysis for the Assessment of Sarcopenia in Patients with Cancer: A Systematic Review. *Oncologist.* 2020;25(2):170-182.
220. Farias CL, Campos DJ, Bonfin CM, Vilela RM. Phase angle from BIA as a prognostic and nutritional status tool for children and adolescents undergoing hematopoietic stem cell transplantation. *Clin Nutr.* 2013;32(3):420-425.
221. Franco-Oliva A, Avila-Nava A, Rodriguez-Aguilar EA, et al. Association between phase angle and the nutritional status in pediatric populations: a systematic review. *Front Nutr.* 2023;10:1142545.
222. Kelly AS, Barlow SE, Rao G, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation.* 2013;128(15):1689-1712.
223. Walters M, Mowbray C, Jubelirer T, et al. A bilingual dietary intervention early in treatment is feasible and prevents weight gain in childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2021;68(5):e28910.

224. Zhang Y, Zhou F, Guan J, Zhou L, Chen B. Action Mechanism of Metformin and Its Application in Hematological Malignancy Treatments: A Review. *Biomolecules.* 2023;13(2).
225. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2014;384(9945):766-781.
226. Soltani M, Zhao Y, Xia Z, Ganjalikhani Hakemi M, Bazhin AV. The Importance of Cellular Metabolic Pathways in Pathogenesis and Selective Treatments of Hematological Malignancies. *Front Oncol.* 2021;11:767026.
227. Pan J, Chen C, Jin Y, et al. Differential impact of structurally different anti-diabetic drugs on proliferation and chemosensitivity of acute lymphoblastic leukemia cells. *Cell Cycle.* 2012;11(12):2314-2326.
228. Biondani G, Peyron JF. Metformin, an Anti-diabetic Drug to Target Leukemia. *Front Endocrinol (Lausanne).* 2018;9:446.
229. Trucco M, Barredo JC, Goldberg J, et al. A phase I window, dose escalating and safety trial of metformin in combination with induction chemotherapy in relapsed refractory acute lymphoblastic leukemia: Metformin with induction chemotherapy of vincristine, dexamethasone, PEG-asparaginase, and doxorubicin. *Pediatr Blood Cancer.* 2018;65(9):e27224.
230. Buono R, Alhaddad M, Fruman DA. Novel pharmacological and dietary approaches to target mTOR in B-cell acute lymphoblastic leukemia. *Front Oncol.* 2023;13:1162694.
231. Shah UA, Iyengar NM. Plant-Based and Ketogenic Diets As Diverging Paths to Address Cancer: A Review. *JAMA Oncol.* 2022;8(8):1201-1208.
232. Spreafico F, Murelli M, Timmons BW, Massimino M, Barr R. Sport activities and exercise as part of routine cancer care in children and adolescents. *Pediatr Blood Cancer.* 2019;66(8):e27826.
233. Wilson CL, Stratton K, Leisenring WL, et al. Decline in physical activity level in the Childhood Cancer Survivor Study cohort. *Cancer Epidemiol Biomarkers Prev.* 2014;23(8):1619-1627.
234. Cohen J, Collins L, Gregerson L, Chandra J, Cohn RJ. Nutritional concerns of survivors of childhood cancer: A "First World" perspective. *Pediatr Blood Cancer.* 2020;67 Suppl 3:e28193.
235. Jarvholm K, Janson A, Peltonen M, et al. Metabolic and bariatric surgery versus intensive non-surgical treatment for adolescents with severe obesity (AMOS2): a multicentre, randomised, controlled trial in Sweden. *Lancet Child Adolesc Health.* 2023;7(4):249-260.
236. Jobanputra R, Sargeant JA, Almaqhawi A, et al. The effects of weight-lowering pharmacotherapies on physical activity, function and fitness: A systematic review and meta-analysis of randomized controlled trials. *Obes Rev.* 2023;24(4):e13553.
237. Gou H, Zhai Y, Guo J. Efficacy and safety of liraglutide for weight management in children and adolescents: a systematic review and meta-analysis of randomized controlled trials. *Eur J Pediatr.* 2023.