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ORIGINAL ARTICLE

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Impact of body mass index on relapse in children with acute lymphoblastic leukemia treated according to Nordic treatment protocols

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Abstract

Objectives: High body mass index (BMI) is associated with poorer survival in childhood acute lymphoblastic leukemia (ALL), but the actual impact on the risk of relapse still needs to be clarified. We evaluated the impact of BMI at diagnosis on the risk of relapse in children with ALL treated according to Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocols.

Method: In a multicenter study, we collected data on BMI at diagnosis and outcome of 2558 children aged 2.0-17.9 years diagnosed between 1992 and 2016. Patients were divided into four groups according to International Obesity Task Force (IOTF) childhood BMI cut-offs: underweight, <17; healthy weight, 17-25; overweight, 25-30; and obese, ≥30 kg/m^2.

Results: In Cox multivariate regression analyses, an increased risk of relapse was observed in children aged 10-17.9 years with unhealthy BMI at diagnosis (underweight hazard ratio HR: 2.90 [95% confidence interval: 1.24-6.78], $P = .01$; overweight, HR: 1.95 [1.11-3.43], $P = .02$, and obese HR: 4.32 [95% 2.08-8.97], $P < .001$), compared to children with healthy weight. BMI had no impact on relapse in children under 10 years of age.

Conclusion: High BMI, and especially obesity at diagnosis, is an independent adverse prognostic factor for relapse in older children with ALL.

KEYWORDS
acute lymphoblastic leukemia, body mass index, children, obesity, survival

1 | INTRODUCTION

Today, approximately 90% of children with acute lymphoblastic leukemia (ALL) can be cured with modern treatment protocols.[1,2] Individualized treatment strategies are needed to address the adverse outcome in high-risk subgroups. Current risk stratification is based on the disease characteristics at diagnosis, genetic changes in the leukemic cells, and early treatment response. Age is also often considered in risk stratification.

Adipose tissue is an active metabolic and endocrine organ. The amount of body fat, for which body mass index (BMI) is a surrogate marker, may influence the pharmacokinetics of antileukaemic agents, modify immunity against infections, and affect the risk of treatment related toxicity. BMI at diagnosis affect outcomes of ALL treatment and could be an important predictive factor in childhood ALL. Two meta-analyses studying the impact of BMI on outcomes concluded that high BMI at diagnosis is associated with a poorer overall (OS) and event-free survival (EFS) in pediatric ALL,[3,4] although both conclude that the impact of BMI on the risk of relapse still needs to be clarified. Findings from earlier studies on the risk of relapse have reported inconsistent results, some studies reporting a tendency toward a higher relapse rate in overweight and obese children,[5-7] while others found no association.[8,9] One large study from the Children's Cancer Group found a higher risk of relapse in obese patients compared with non-obese children.[6] In their study, obesity was more strongly associated with the relapse risk in preadolescent and adolescent patients than in younger patients. Furthermore, underweight has also been associated with a higher relapse risk.[10]

BMI may be an additional independent risk factor for adverse outcome to consider in risk stratification for treatment assignment in ALL protocols. Knowledge on the reasons for adverse outcome with unhealthy BMI is scarce. We hypothesized that children in extreme BMI categories at diagnosis are more likely to relapse. This retrospective study investigated the impact of BMI at diagnosis on relapse in children with ALL treated according to Nordic treatment protocols.

2 | METHODS

2.1 | Study cohort

We included all children aged 2.0-17.9 years at diagnosis of ALL, between 1992 and 2016 and enrolled in the Nordic Society of Paediatric Hematology and Oncology (NOPHO) ALL protocols 1992, 2000, and 2008. Surviving patients were followed until the end of December 2017. Patients with missing data on BMI and non-protocol patients (acute leukemia of ambiguous lineage, Philadelphia-positive ALL, mature B-cell leukemia, and patients with Down syndrome) were excluded as well as those below 2 years old at diagnosis because the BMI cut-offs used in this study are defined from 2 years of age. The study was approved by the Regional Ethical Review Board in Stockholm (reference number 2018/1888-31).

2.2 | Treatment protocols

The children were treated in one of five Nordic countries (Sweden, Norway, Denmark, Finland, and Iceland) according to the NOPHO ALL1992,[11,12] ALL2000,[13,14] or ALL2008[15,16] protocols, which have been described in detail earlier. Patients from Lithuania and Estonia were included starting from July 2008 (NOPHO ALL2008). In brief, the risk stratification included age (for the two first protocols only), white blood cell (WBC) count, central nervous system (CNS) status, immunophenotype, and cytogenetics at diagnosis and initial treatment response.[13-15] The children were divided into non-high (ie, standard and intermediate risk) and high-risk groups. Patients treated according to the NOPHO ALL1992 protocol were classified into the high-risk group based on WBC count >50 × 10^9/L at diagnosis, T-cell immunophenotype, CNS or testicular involvement, the presence of t(4;11)(q21;q23) or poor response to treatment. In the NOPHO ALL2000 protocol, the risk assignment was similar to the ALL1992 protocol, with the addition of any KMT2A-rearrangement, hypodiploidy, and t(1;19) as high-risk criteria. In the 2008 protocol, high-risk patients were defined as those with B-cell-precursor (BCP) ALL with WBC > 100 × 10^9/L at diagnosis or T-cell immunophenotype and MRD > 0.1% at day 29, or any patient with poor response (MRD > 5% on treatment day 29 or ≥0.1% day 79) or unfavorable cytogenetics (KMT2A rearrangement and/or hypodiploidy). CNS disease was defined as >5 × 10^6/L leukocytes in cerebrospinal fluid and leukemic blasts on cytospin or neurological symptoms such as cranial nerve palsy. Patients dying before response evaluation during induction (induction deaths) were for the purpose of this study divided to non-high-risk or high-risk groups according to their risk stratification at diagnosis. The body surface area (BSA) was used for dosing in all systemic chemotherapies, but a maximum dose of 2 mg (NOPHO ALL1992) or 2.5 mg (NOPHO ALL2000 and ALL2008) was applied for vincristine.

2.3 | Register data

This study is based on data retrieved from the NOPHO registry. The registry includes prognostic risk factors at diagnosis, such as WBC count, immunophenotype, cytogenetics, and CNS status. Additional data provided were assessment of response to induction at day 29 by morphology (NOPHO ALL1992 and ALL2000) or by minimal residual disease (MRD) (NOPHO ALL2008) and the administered risk group adapted treatment and follow-up data such as time of relapse, death, secondary malignant neoplasm (SMN), and last follow-up in continuous complete remission. Treatment related mortality (TRM) was defined as death during induction or death during first complete remission (DCR1).

BMI, based on registered height and weight at diagnosis, was calculated and classified according to international age- and sex-adjusted (International Obesity Task Force, IOTF) BMI cut-offs, in our study referred to as IOTF cut-offs, set by Cole et al for thinness and the IOTF for overweight and obesity.[17,18] The BMI classifications are based on smoothed sex-specific IOTF curves, which provide cut-offs corresponding to BMI of <17 kg/m^2 for thinness/underweight, >25 kg/m^2 for overweight and ≥30 kg/m^2 for obesity at 18 years of age. The BMI cut-offs are tracked back to define BMI values for younger ages with centiles constructed using the LMS method[19] based on 6 nationally representative data sets. The patients were classified into four groups using IOTF cut-offs for underweight, overweight, and obesity. BMI values were also transformed into standard deviation scores (SDS) for further analyses.[20] To make the study more comparable with other studies, survival analyses were repeated using classification according to the WHO growth references. The WHO reference uses cut-offs based on standard deviation scores, where −2 SDS from the age-sex-specific growth reference median is classified as underweight. The cut-off terminology for overweight and obesity differs for children below and above 5 years. In children below 5 years of age, SDS between +1 and 2 is defined as risk of overweight and over +2 SDS as overweight (including obesity).[21] We have defined obesity as over +3 SDS in the younger children. In the children of 5-18 years, +1 SDS and +2 SDS are used to define overweight and obesity, respectively.[22]

2.4 | Statistical analysis

The association between BMI category and other categorical variables was explored using chi-square test. The primary outcome of interest was the risk of relapse in different weight categories. OS was defined as days from diagnosis until death from any cause. EFS was calculated from the time of diagnosis to relapse, secondary malignancy, or death in complete remission. Those alive and event free at the last follow-up were also censored at that time point. Patients who underwent hematopoietic stem cell transplantation were censored at the date of transplantation. The Kaplan-Meier (KM) method was used to estimate the probability of cumulative incidence of relapse and OS in different BMI categories. Cumulative incidence of relapse was calculated and visualized with death and SMN as competing risks.[23] Cox proportional hazard regression analyses were used to analyze the effect of BMI on the primary outcome relapse, compared to children with healthy BMI, but also the potential effect on OS, EFS, induction death, SMN, DCR1, and TRM. Multivariate Cox proportional hazard models were constructed adjusting for sex, age, protocol, and risk group. The linearity assumption of the association between log HR of relapse and BMI SDS entered as a continuous variable in a Cox Proportional Hazards Model was tested using a model with restricted cubic splines. Statistical analyses were performed using SPSS version 25.0 for Windows (SPSS Inc, Chicago, IL) and R version 3.5.0. Two-sided *P*-values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Of the 3941 children with ALL, 1383 (35%) were excluded due to missing BMI, most of whom (1255 patients; 91%) were treated with the oldest ALL protocol, NOPHO ALL1992. There were no statistically significant differences in sex, age, risk group, immunophenotype, and CNS status at diagnosis between children with and without registered BMI.

Of the 2558 children included in the study cohort, 123 (4.8%) were classified as underweight, 2113 (82.6%) as healthy weight, 258 (10.1%) as overweight, and 64 (2.5%) as obese, according to IOTF cut-offs, at the time of diagnosis (Table 1). The median age at diagnosis was 5.1 years (range, 2.0-17.9 years).

Overweight and obese patients were more likely to belong to the older age group, 10 to 17.9 years ($P < .001$), or to be stratified into the high-risk group ($P = .008$). There were more patients from the older age group in the high-risk group compared to the younger age group (36.8% vs 18.7%). The higher frequency for obese and overweight patients to be stratified into the high-risk group was not significant when analyzing the patients in the two separate age groups (Table S1 and S2). There were no statistically significant differences in sex, immunophenotype, CNS status at diagnosis, treatment response at end of induction, or hematopoietic stem cell transplantation between the different BMI categories. The median follow-up time was 6.6 years (range, 5 days-23.9 years) among patients who were alive at last recorded follow-up.

Obese patients had significantly poorer outcomes than those with healthy BMI. After adjustment in multivariate Cox regression analyses for age, protocol, risk group, and sex, obese children had a tendency to higher risk of relapse (HR: 1.72, 95% CI: 0.98-3.00, $P = .06$), and a significant higher risk of death (OS; HR: 3.03, 95% CI: 1.66-5.53, $P < .001$), and lower EFS (HR: 2.04, 95% CI: 1.30-3.22, $P = .002$), than healthy weight children (Table 2).

Differences in outcome between BMI categories, according to IOTF cut-offs, were only observed in the older children (n = 578), after separating the cohort into two age groups (younger age group 2-9.9 years and older age group 10-17.9 years). No differences in survival, nor relapse, between the BMI categories were found in

TABLE 1 Baseline patient characteristics

	Overall population	Underweight BMI < 17 kg/m^2	Healthy weight BMI 17-<25 kg/m^2	Overweight BMI 25-<30 kg/m^2	Obese BMI ≥ 30 kg/m^2	
	No. (%)					
Cohort:	2558	123 (4.8)	2113 (82.6)	258 (10.1)	64 (2.5)	
Age at diagnosis						<.001
Median age	5.1 (2.0-17.9)	4.2	5.0	6.3	8.2	
2-9	1980 (77.4)	102 (82.9)	1656 (78.4)	181 (70.2)	41 (64.1)	
10-17	578 (22.6)	21 (17.1)	457 (21.6)	77 (29.8)	23 (35.9)	
Sex						.814
Male	1410 (55.1)	65 (52.8)	1171 (55.4)	137 (53.1)	37 (57.8)	
Female	1148 (44.9)	58 (47.2)	942 (44.6)	121 (46.9)	27 (42.2)	
NOPHO protocol[a]						.655
1992, 2000	1209 (47.3)	62 (50.4)	1004 (47.5)	114 (44.2)	29 (45.3)	
2008	1349 (52.7)	61 (49.6)	1109 (52.5)	144 (55.8)	35 (54.7)	
Risk group						.008
Standard-/intermediate risk	1967 (76.9)	104 (84.6)	1636 (77.4)	181 (70.2)	46 (76.9)	
High-risk	591 (23.1)	19 (15.4)	477 (22.6)	77 (29.8)	18 (28.1)	
White blood cell count (×109/L) at diagnose						.604
<50	2033 (79.5)	103 (83.7)	1681 (79.6)	203 (78.7)	46 (71.9)	
>50 - <100	221 (8.6)	8 (6.5)	180 (8.5)	26 (10.1)	7 (10.9)	
>100	304 (11.9)	12 (9.8)	252 (11.9)	29 (11.2)	11 (17.2)	
Immunophenotype						.222
B lineage (90.3%)	2248 (87.9)	115 (93.5)	1855 (87.8)	223 (86.4)	55 (87.9)	
T cell (9.7%)	310 (12.1)	8 (6.5)	258 (12.2)	35 (13.6)	9 (12.1)	
Response MRD, day 29[b]						.281
<0.1%	1263 (68.1)	60 (69.8)	1046 (68.2)	129 (68.6)	28 (59.6)	
0.1%-5%	487 (26.3)	25 (29.1)	402 (26.2)	44 (23.4)	16 (34.0)	
>5%	104 (5.6)	1 (1.2)	85 (5.5)	15 (8.0)	3 (6.4)	
Unknown/Missing data	704	37	580	70	16	
Cytogenetics[c]						.077
Normal	314 (12.3)	12 (9.8)	252 (11.9)	44 (17.1)	6 (9.4)	
Low risk	1214 (47.5)	68 (55.3)	1021 (48.4)	102 (39.5)	23 (35.9)	
Intermediate risk	223 (8.7)	9 (7.3)	185 (8.8)	23 (8.9)	6 (9.4)	

(Continues)

TABLE 1 (Continued)

	Overall population	Underweight BMI < 17 kg/m^2	Healthy weight BMI 17-<25 kg/m^2	Overweight BMI 25-<30 kg/m^2	Obese BMI ≥ 30 kg/m^2	
	No. (%)					
High-risk	91 (3.6)	5 (4.1)	67 (3.2)	15 (5.8)	4 (6.3)	
Other	397 (15.5)	17 (13.8)	325 (15.4)	41 (15.9)	14 (21.9)	
No result/missing data	316 (12.4)	12 (9.8)	260 (12.3)	33 (12.8)	11 (17.2)	
Hematopoietic stem cell transplantation						.420
No	2250 (88.0)	111 (90.2)	1861 (88.1)	220 (85.3)	58 (90.6)	
Yes	308 (12.0)	12 (9.8)	252 (11.9)	38 (14.7)	6 (9.4)	
CNS disease						.180
No	2475 (96.8)	119 (96.7)	2113 (97.0)	248 (96.1)	59 (92.2)	
Yes	83 (3.2)	4 (3.3)	64 (3.0)	10 (3.9)	5 (7.8)	

Note: Pearson´s chi-square test for distribution of predictors across BMI categories. *P*-values <.05 are shown in bold.

[a]NOPHO, Nordic Society of Paediatric Oncology and Haematology.

[b]MRD (minimal residual disease), day 29 is a response evaluation that started with the NOPHO 2008 protocol.

[c]Cytogenetics. Low risk: hyperdiploidy, t(12;21); Intermediate risk: t(1;19), dic(9;21), iAmp21. High risk; t(9;22), hypodiploidy, MLL/11q23.

the younger cohort (n = 1980). Of the older children with obesity 39.1% (n = 9) relapsed, compared to 11.4% (n = 52) children with healthy BMI, 28.6% (n = 6) with underweight children and 20.8% (n = 16) with overweight (Table 3). In the multivariate Cox regression analyses, adjusted for age, protocol, risk group, and sex in the older children, obese children had a higher risk of relapse (HR: 4.32, 95% CI: 2.08-8.97, $P < .001$) as well as overweight (HR: 1.95, 95% CI: 1.11-3.43, $P = .02$) and underweight children (HR: 2.90, 95% CI: 1.24-6.78, $P = .01$), compared to healthy weight children (Table 2). The site of relapse did not differ significantly between the BMI categories.

In the same age group, the obese children had worse OS (HR: 4.91, 95% CI: 2.20-11.05, $P < .001$) and EFS (HR: 4.00, 95% CI: 2.13-7.54, $P < .001$) than healthy weight children.

Kaplan-Meier survival analysis in the older age group indicated statistically significant differences in the cumulative probability of relapse (log rank; $P < .001$) and the probability of OS ($P < .001$) between obese and healthy weight children (Figure 1A-D).

The association between BMI SDS as a continuous variable and the log HR for relapse in the older age group demonstrated that it is beneficial for both underweight and obese children to be closer to healthy weight (Figure 2). The association between BMI-SDs with relapse remained significant in the model after adjusting for age at diagnosis as a continuous variable.

3.2 | Events, death and toxicities

We analyzed SMN, (22 events) induction death (24 events), and DCR1 (43 events) in children aged 2.0-17.9 years separately in multivariate hazard ratio analysis adjusting for sex, age, protocol, and risk group. When divided into different BMI categories, the number of events in each group was small, but overweight and obese patients indicated a higher risk of SMN compared to healthy weight patients (HR: 4.66, 95% CI: 1.71-12.64, $P = .003$; HR: 11.56, 95% CI: 3.18-42.12, $P < .001$, respectively, Table 2). There was no significant association between induction death or DCR1 and BMI categories TRM was reported in two (1.6%) of 123 underweight patients, 51 (2.4%) of 2113 patients with healthy weight, 10 (3.9%) of 258 overweight, and four (6.3%) of 64 obese children. There was no association with risk of TRM in the extreme BMI categories of obese (HR: 2.43, 95% CI: 0.87-6.76, $P = .09$) or underweight patients (HR: 0.82, 95% CI: 0.20-3.38, $P = .78$) compared to healthy weight patients. Due to the small number of events for induction death, DCR1, SMN and TRM, multivariate Cox regression analyses stratified into younger and older age groups were not conclusive.

To study how the chosen international BMI cut-offs effected the results, the analyses were also performed using classification and cut-offs based on WHO growth references. With WHO cut-offs, 77 (3.0%) were classified as underweight, 1928 (75.4%) as healthy weight, 426 (16.7%) overweight, and 127 (5.0%) children as obese. The multivariate Cox regression survival analyses showed similar associations with both methods (Table 4). However, the overweight and obese patients had a

TABLE 2 Univariate and 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*
Patients aged 2.0-17.9 y								
Univariate Analysis								
Relapse risk	0.87 (0.56-1.63)	.96	1.09 (0.75-1.58)	.66	2.11 (1.21-3.68)	.009	1.27 (0.92-1.75)	.14
Overall survival	0.61 (0.23-1.65)	.33	1.38 (0.84-2.27)	.20	3.90 (2.14-7.07)	<.001	1.86 (1.24-2.78)	.003
Event-free survival	0.98 (0.61-1.58)	.95	1-31 (0.96-1.78)	.08	2.52 (1.61-3.39)	<.001	1.53 (1.17-1.99)	.002
Multivariate Analysis[a]								
Relapse risk	1.06 (0.62-1.81)	.85	1.01 (0.70-1.47)	.95	1.72 (0.98-3.00)	.06	1.15 (0.83-1.59)	.39
Overall survival	0.74 (0.27-2.02)	.56	1.12 (0.68-1.85)	.66	3.03 (1.66-5.53)	<.001	1.50 (0.99-2.25)	.05
Event-free survival	1.10 (0.68-1.77)	.70	1.20 (0.88-1.63)	.25	2.04 (1.30-3.22)	.002	1.37 (1.05-1.78)	.02
Induction death[b]	1.12 (0.15-8.45)	.91	0.55 (0.13-2.35)	.42	1.51 (0.20-11.24)	.69	0.70 (0.21-2.35)	.92
Death first complete remission[b]	0.67 (0.75-2.59)	.69	1.63 (0.75-3.59)	.22	2.77 (0.84-9.20)	.10	2.38 (1.20-4.73)	.01
Secondary malignant neoplasm[b]	3.23 (0.71-14.68)	.13	4.66 (1.71-12.64)	.003	11.56 (3.18-42.12)	<.001	5.95 (2.47-14.37)	<.001
Patients aged 2.0-9.9 y								
Univariate analysis								
Relapse risk	0.64 (0.32-1.30)	.21	0.72 (0.43-1.22)	.23	0.89 (0.33-2.40)	.82	0.75 (0.47-1.21)	.25
Overall survival	0.59 (0.19-1.86)	.37	1.05 (0.53-2.09)	.89	2.06 (0.75-5.61)	.16	1.23 (0.69-2.22)	.48
Event-free survival	0.80 (0.44-1.39)	.40	0.97 (0.64-1.47)	.89	1.43 (0.71-2.90)	.32	1.05 (0.73-1.52)	.77
Multivariate Analysis[a]								
Relapse risk	0.71 (0.35-1.45)	.35	0.71 (0.42-1.20)	.20	0.70 (0.26-1.88)	.48	0.71 (0.44-1.13)	.15
Overall survival	0.69 (0.22-2.20)	.53	0.89 (0.45-1.78)	.75	1.70 (0.62-4.66)	.30	1.05 (0.58-1.88)	.88
Event-free survival	0.87 (0.49-1.56)	.65	0.93 (0.62-1.41)	.75	1.15 (0.57-2.33)	.70	0.98 (0.68-1.41)	.91
Patients aged 10.0-17.9 y								
Univariate analysis								
Relapse risk	2.87 (1.21-6.67)	.01	1.99 (1.14-3.49)	.02	4.81 (2.36-9.79)	<.001	2.52 (1.56-4.06)	<.001
Overall survival	0.78 (0.11-5.69)	.78	1.83 (0.87-3.87)	.11	6.24 (2.85-13.66)	<.001	2.74 (1.51-4.97)	.001
Event-free survival	2.15 (0.93-4.96)	.07	2.07 (1.28-3.35)	.003	4.67 (2.52-8.66)	<.001	2.57 (1.70-3.88)	<.001
Multivariate analysis[a]								
Relapse risk	2.90 (1.24-6.78)	.01	1.95 (1.11-3.43)	.02	4.32 (2.08-8.97)	<.001	2.41 (1.49-3.91)	<.001
Overall survival	0.99 (0.13-7.34)	.99	1.61 (0.76-3.41)	.21	4.91 (2.20-11.05)	<.001	2.34 (1.29-4.26)	.005
Event-free survival	2.26 (0.98-5.24)	.06	1.98 (1.22-3.21)	.006	4.00 (2.13-7.54)	<.001	2.40 (1.58-3.63)	<.001

[a]The multivariate analyses are adjusted for age, protocol, risk group and sex.

[b]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.

higher risk for DCR1 (HR: 2.17, 95% CI 1.11-4.26, $P = .02$ and HR: 2.90, 95% CI 1.10-7.60, $P = .03$), which was not statistically significant in the analyses using the international cut-offs.

4 | DISCUSSION

Limited evidence exists on the association between BMI and relapse in children with ALL. This study demonstrates that being overweight or obese at diagnosis is associated with higher risk of relapse in adolescent ALL, treated according to Nordic leukemia protocols. Our results are in line with a large study from the Children's Cancer group that also found obesity at time of diagnosis to be an independent predictor of relapse and worse EFS in older children.[6] Similarly, a meta-analysis concluded that overweight and obese BMI was associated with poorer OS and EFS and a tendency to increased risk of relapse in pediatric ALL.[3]

In this study, the increased risk of relapse among the extreme BMI categories, especially the obese patients, was the main reason for the poorer overall survival. In contrast to Orgel el al,[24] we could not

TABLE 3 Differences in relapse and events according to IOTF BMI category in different age groups

Patients aged 2.0-17.9 y	Total nr of events	Underweight n = 123 (%)	Healthy weight n = 2113 (%)	Overweight n = 258 (%)	Obese n = 64 (%)	*P* value
Relapse	305	14 (11.4)	247 (11.7)	31 (10.0)	13 (20.3)	<.001
Deaths	144	4 (2.8)	110 (5.2)	18 (7.0)	12 (18.8)	<.001
Induction death	24	1 (0.8)	20 (0.9)	2 (0.8)	1 (1.6)	
Death in first complete remission	43	1 (0.8)	31 (1.5)	8 (3.1)	3 (4.7)	.05
Secondary malignant neoplasm[a]	22	2 (1.6)	11 (0.5)	6 (2.3)	3 (4.8)	<.001
Differences in survival and events according to IOTF BMI category in different age groups						
Patients aged 2.0-9.9 y	Total nr	**Underweight** n = 102 (%)	**Healthy weight** n = 1656 (%)	**Overweight** n = 181 (%)	**Obese** n = 41 (%)	***P* value**
Relapse	222	8 (7.8)	195 (11.8)	15 (8.3)	4 (9.8)	.35
Deaths	96	3 (2.9)	80 (4.8)	9 (5.0)	4 (9.8)	.50
Induction death	19	1 (1.0)	15 (0.9)	2 (1.1)	1 (1.0)	
Death in first complete remission	28	1 (1.0)	21 (1.3)	5 (2.8)	1 (2.4)	.38
Secondary malignant neoplasm	17	2 (2.0)	10 (0.6)	3 (1.7)	2 (4.9)	.01
Patients aged 10.0-17.9 y	Total nr	**Underweight** n = 21 (%)	**Healthy weight** n = 457 (%)	**Overweight** n = 77 (%)	**Obese** n = 23 (%)	***P* value**
Relapse	83	6 (28.6)	52 (11.4)	16 (20.8)	9 (39.1)	<.001
Deaths	48	1 (4.8)	30 (6.6)	9 (11.7)	8 (34.8)	<.001
Induction death	5	0	5 (1.1)	0	0	
Death in first complete remission	15	0	10 (2.2)	3 (3.9)	2 (8.7)	
Secondary malignant neoplasm	5	0	1 (0.2)	3 (3.9)	1 (4.3)	

Note: P value: Pearson´s chi-square test for distribution of events across BMI weight category.

[a]Secondary malignant neoplasm: 5 patients developed myelodysplastic syndrome (MDS), 8 acute myeloid leukemia (AML), 8 "other" malignancy and 1 patient was not specified.

detect a difference between the different weight categories when evaluating how BMI influences response to therapy. However, MRD results were available only for the NOPHO 2008 protocol patients, decreasing the power of this analysis. The obese and underweight patients did not have significantly increased TRM in our study. In contrast, a recent study of 373 children with ALL, 58 of whom were obese, showed that obese children had worse OS compared to non-obese likely due to TRM, but there were no association to relapse.[25] In line with other previous studies exploring TRM, BMI in our study did not influence the risk of DCR1.[9,10,25] The lack of power analyzing rare events such as DCR1 and induction death may explain the difficulties in detecting statistically significant differences. The effect of BMI at diagnosis on TRM remains controversial in childhood ALL. In our study, overweight and obese children had higher risk of secondary malignancy. One explanation could be the correlation between obesity and cancer driven by the adipose tissue,[26] possibly contributing to an added risk for SMN. Nevertheless, due to small number of events, this finding needs to be interpreted with caution.

We also found that older underweight children had a higher relapse risk and a tendency to poorer EFS than those with healthy BMI. In den Hoed's cohort,[10] underweight patients aged 2-17 years at diagnosis had higher risk of relapse. This was observed only in older patients in the current study and is of great importance in low- and middle-income income countries where underweight is more common. However, den Hoed et al similarly found that despite the higher relapse rate, the OS of underweight patients did not differ from that of the other BMI groups. In the study by the Children's Oncology Group,[27] patients who were underweight or obese and remained in their BMI category for more than 50% of the time until maintenance, the risk for relapse or death was almost twice as high compared to those with normal weight throughout the treatment period; normalization of BMI during the same period resulted in decreased risk comparable to never being obese or underweight. Unfortunately, we only had the BMI at diagnosis and could not compare whether changes in weight during therapy are associated with survival outcome. Also, body composition changes with therapy with loss of skeletal muscle and increased muscle-associated fat; this may contribute to higher risk of cardiovascular and metabolic disorders in adulthood.[28,29]

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 may contribute to the conflicting results on this topic. A European Childhood Obesity Group guideline[30] recommends using the International Obesity Task Force (IOTF)[17] and the World Health Organization (WHO)[21,31] definitions to assess childhood overweight and obesity, and definitions by Cole et al[18] and the WHO for the prevalence of thinness. In previous studies investigating the prognostic impact of thinness, overweight, and obesity in children with ALL,[6,8,9,24,25,27,32] the cut-offs used were those from

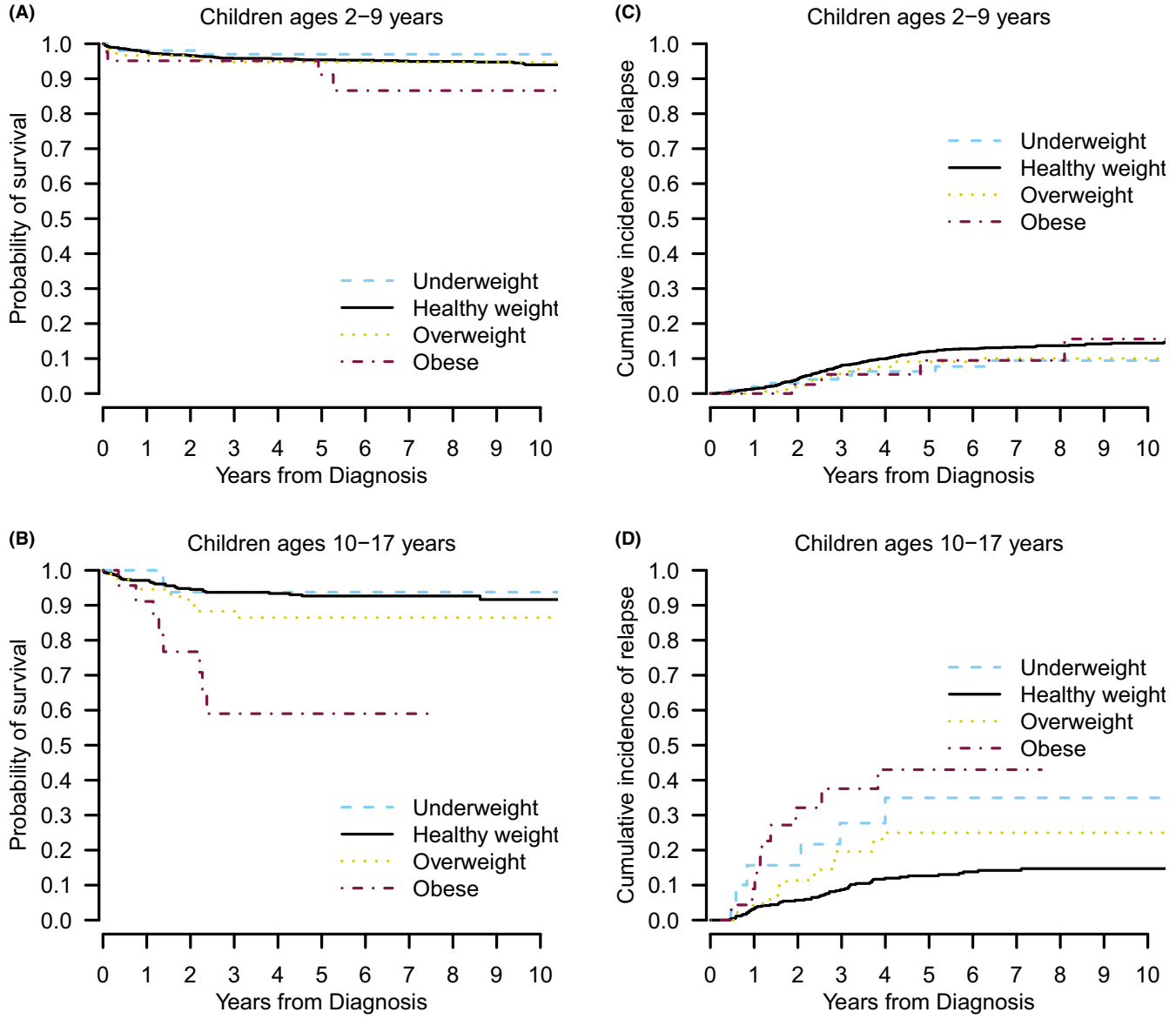

FIGURE 1 Kaplan-Meier curves illustrating the effect of BMI classification on overall survival (A and B) and cumulative incidence of relapse (C and D) in younger children (age 2.0-9.9 y) (A and C), and older children (age 10.0-17.9 y) (B and D). For the assessment of cumulative incidence of relapse, death and secondary malignant neoplasm (SMN) were treated as competing risks

nationally representative data for the USA (ie, Centers for Disease Control and Prevention). Other studies have categorized BMI using SD scores with data from national[10] or WHO growth charts.[7] These differences in methodology make comparison between different studies difficult. In addition, we compared obese or overweight/obese patients with patients with healthy BMI, whereas many studies have compared obese or overweight patients with the remaining patients (ie, underweight and healthy weight patients). Our study cohort has fewer children who were overweight and obese than earlier studies on the subject. The lower prevalence of overweight and obesity in this study is partly attributed to the use of the international childhood BMI cut-offs by IOTF, which resulted in a lower overweight and obesity prevalence compared to when the WHO cut-offs were used.[30] Furthermore, most studies were conducted in the USA, where the incidence of obesity is higher than in northern Europe.[33-35] In addition, it is important to note that BMI as an anthropomorphic measure, a surrogate for body composition and nutritional status, and does not distinguish fat and lean muscle mass distribution.

Several hypotheses for biological mechanisms of the effect of obesity and underweight on leukemia therapy have been suggested. Pharmacokinetics is affected by multiple factors, such as plasma protein binding capacity, water or lipid solubility of the compound, liver metabolism, and the function of the excretion pathway. However, studies comparing the pharmacokinetics of various drugs in adult or pediatric obese patients with normal weight controls reported conflicting results, and few studies have been performed in underweight patients.[8,9,25,27] A study in St Jude Children's Research Hospital

found no difference in intracellular levels of thioguanine and methotrexate metabolites or systemic clearance of methotrexate, teniposide, etoposide, and cytarabine between four BMI groups in pediatric ALL.[9] In vivo and in vitro mice models showed that obesity increased the relapse risk after vincristine monotherapy, with the adipocytes causing resistance to chemotherapy-induced apoptosis.[36] Another preclinical study with daunorubicin and vincristine demonstrated migration of leukemic blast cells into a protective microenvironment in the adipose tissue.[37] The findings suggest that migration of leukemic blasts into adipose tissue could contribute to drug resistance and, potentially, to relapse. Ehsanipour et al also suggested that adipocytes contributed to a protective leukemia microenvironment due to a release of glutamine in the bone marrow, causing leukemia cell resistance to asparaginase.[38]

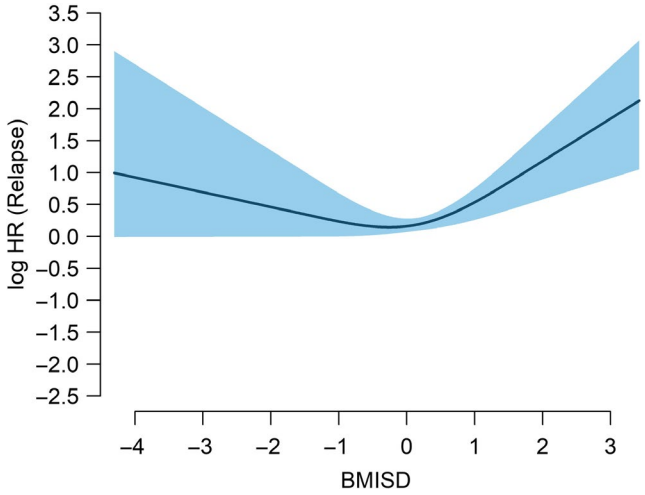

FIGURE 2 Estimated association between BMI standard deviation score (BMI SDS) as a continuous variable in a Cox proportional hazards model with restricted cubic splines, in children aged 10.0-17.9 y at diagnosis and the log HR for time to relapse. The U-shaped association between BMI SDS and log HR of relapse show that the risk appears to increase below and above a BMI SDS of around zero.

The mechanisms underlying the association between unhealthy BMI and ALL outcome are most likely multifactorial. Even though our and previous studies show association, there may be common underlying predisposing factors rather than direct causality. More studies are needed to determine the underlying mechanism behind the impact of obesity, overweight, and underweight on survival in patients with ALL. If the increased relapse rate is due to toxicity and compromised treatment intensity, treatment modification with personalization of therapy, and considering immunological treatment already in first line, could be an option. It is also important to highlight that extreme BMI is a modifiable prognostic risk factor, and more studies on early interventions (nutrition and physical activity) during treatment are needed. A high BMI at the beginning of therapy, as well as weight gain during induction, is a strong predictor of overweight and obesity at the end of therapy.[39,40] Adequate and appropriate nutrition is important and may decrease toxicity and improve quality of life and outcome.

In conclusion, our findings confirm that obesity at diagnosis is an independent prognostic risk factor in ALL, particularly in older children. The mechanisms underlying poorer outcome is yet

TABLE 4 Multivariate hazard ratios for relapse, event-free survival and survival according to the WHO BMI cut-offs

	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*
Patients aged 2-17.9 y								
Relapse	1.42 (0.81-2.49)	.22	0.91 (0.66-1.26)	.58	1.24 (0.78-1.98)	.33	1.01 (0.76-1.33)	.97
Overall Survival	1.07 (0.39-2.92)	.89	1.29 (0.85-1.97)	.24	2.13 (1.23-3.67)	.007	1.48 (1.03-2.12)	.03
Event-free survival	1.33 (0.79-2.24)	.28	1.14 (0.88-1.49)	.32	1.46 (0.99-2.15)	.06	1.21 (0.96-1.52)	.11
Induction death	2.02 (0.26-15.52)	.50	0.86 (0.29-2.55)	.79	0.59 (0.08-4.45)	.61	0.79 (0.29-2.15)	.64
Death first complete remission	no event		2.17 (1.11-4.26)	.02	2.90 (1.10-7.60)	.03	2.34 (1.27-4.29)	.006
Secondary malignant neoplasm	2.17 (0.28-16.89)	.46	3.14 (1.22-8.11)	.02	5.00 (1.38-18.10)	.01	3.53 (1.50-8.34)	.004
Patients aged 10-17.9 y[a]								
Relapse	2.41 (1.33-5.11)	.02	1.70 (0.95-3.04)	.08	3.36 (1.77-6.37)	<.001	2.17 (1.35-3.49)	.02
Overall survival	1.34 (0.31-5.69)	.70	1.96 (0.96-3.99)	.06	3.91 (1.81-8.42)	<.001	2.46 (1.37-4.43)	.003
Event-free survival	1.99 (0.95-4.17)	.07	1.96 (1.21-3.18)	.006	3.39 (1.95-5.91)	<.001	2.35 (1.57-3.53)	<.001

Note: Numbers of patients: 77 (3.0%) children were underweight, 1928 (75.4%) healthy weight, 426 (16.7%) overweight and 127 (5.0%) obese. Adjusted for age, protocol, risk group and sex.

[a]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.

unclear, and our study suggests higher relapse rate as the main factor. The increasing prevalence of worldwide overweight and obesity[41] underlines the need for assessment of its risks in children with ALL.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. Butturini AM, Dorey FJ, Lange BJ, et al. Obesity and outcome in pediatric acute lymphoblastic leukemia. *J Clin Oncol*. 2007;25(15):2063-2069.
7. Gelelete CB, Pereira SH, Azevedo AM, et al. Overweight as a prognostic factor in children with acute lymphoblastic leukemia. *Obesity (Silver Spring)*. 2011;19(9):1908-1911.
8. 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.
9. 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.
10. 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.
11. Gustafsson G, Schmiegelow K, Forestier E, et al. Improving outcome through two decades in childhood ALL in the Nordic countries: the impact of high-dose methotrexate in the reduction of CNS irradiation. Nordic Society of Pediatric Haematology and Oncology (NOPHO). *Leukemia*. 2000;14(12):2267-2275.
12. Schmiegelow K, Bjork O, Glomstein A, et al. Intensification of mercaptopurine/methotrexate maintenance chemotherapy may increase the risk of relapse for some children with acute lymphoblastic leukemia. *J Clin Oncol*. 2003;21(7):1332-1339.
13. Schmiegelow K, Forestier E, Hellebostad M, et al. Nordic Society of Paediatric H, Oncology. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. *Leukemia*. 2010;24(2):345-354.
14. Vaitkeviciene G, Forestier E, Hellebostad M, et al. High white blood cell count at diagnosis of childhood acute lymphoblastic leukaemia: biological background and prognostic impact. Results from the NOPHO ALL-92 and ALL-2000 studies. *Eur J Haematol*. 2011;86(1):38-46.
15. 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.
16. 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.
17. 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.
18. 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.
19. Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr*. 1990;44(1):45-60.
20. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes*. 2012;7(4):284-294.
21. Group WHOMGRS. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl*. 2006;450:76-85.
22. 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.
23. Gray B. cmprsk: subdistribution analysis of competing risks. R package version 2.2-7. 2014 Available from: https://CRAN.R-project.org/package=cmprsk. Accessed 12 February, 2019.
24. 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.
25. 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.
26. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer*. 2004;4(8):579-591.
27. 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.
28. 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.
29. Mueske NM, Mittelman SD, Wren TAL, Gilsanz V, Orgel E. Myosteatosis in adolescents and young adults treated for acute lymphoblastic leukemia. *Leuk Lymphoma*. 2019;60(13):3146-3153.
30. Rolland-Cachera MF. Childhood obesity: current definitions and recommendations for their use. *Int J Pediatr Obes*. 2011;6(5-6):325-331.

31. 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.
32. 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.
33. Lobstein T, Jackson-Leach R. Child overweight and obesity in the USA: prevalence rates according to IOTF definitions. *Int J Pediatr Obes*. 2007;2(1):62-64.
34. Lobstein T, Frelut ML. Prevalence of overweight among children in Europe. *Obes Rev*. 2003;4(4):195-200.
35. Ahrens W, Pigeot I, Pohlabeln H, et al. Prevalence of overweight and obesity in European children below the age of 10. *Int J Obes (Lond)*. 2014;38(Suppl 2):S99-S107.
36. Behan JW, Yun JP, Proektor MP, et al. Adipocytes impair leukemia treatment in mice. *Cancer Res*. 2009;69(19):7867-7874.
37. 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.
38. 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.
39. 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.
40. 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.
41. 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.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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