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Bariatric interventions in obesity treatment and prevention in pediatric acute lymphoblastic leukemia: a systematic review and meta-analysis

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Abstract

Most children are surviving acute lymphoblastic leukemia (ALL) today. Yet, the emergence of cardiometabolic comorbidities in this population may impact long-term outcomes including the quality of life and lifespan. Obesity is a major driver of cardiometabolic disorders in the general population, and in ALL patients it is associated with increased risk of hypertension, dysglycemia, and febrile neutropenia when compared with lean ALL patients undergoing therapy. This systematic review aims to assess the current evidence for bariatric interventions to manage obesity in children with ALL. The primary outcome for this systematic review was the change in BMI *z*-score with implementation of the interventions studied. Literature searches were conducted in several databases. Ten publications addressing the study question were included in this review, and five studies were used in the meta-analysis to assess the impact of the bariatric interventions on obesity. The BMI *z*-score did not change significantly with the interventions. However, the quality of evidence was low, which precluded the recommendation of their use. In conclusion, prospective, rigorous, adequately powered, and high-quality longitudinal studies are urgently needed to deliver effective lifestyle interventions to children with ALL to treat and prevent obesity. These interventions, if successful, may improves cardiometabolic health outcomes and enhance the quality of life and life expectancy in children with ALL.

Keywords Systematic review · Obesity · Lifestyle intervention · Pediatric acute lymphoblastic leukemia

1 Introduction

Over the past few decades, the revolution in pediatric acute lymphoblastic leukemia (ALL) management has boosted the survival rates of these patients [1]. Strategies credited with improved survival include the use of less-toxic chemotherapies, limitation of radiotherapy use, the screening for therapy-related complications, management of hemorrhage, and infection control [2, 3]. While the drivers of morbidity and mortality were aggressively addressed, new factors

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including obesity are emerging as an increasingly important determinant of morbidity and mortality. Compared to lean pediatric ALL patients undergoing therapy, obese patients are four-times more likely to develop hypertension and dysglycemia and are three times more likely to get febrile neutropenia [4].

Several cohort studies have noted that the risk of cardiovascular diseases including stroke, myocardial infarction, valvular disease, and arrhythmias were linked to anthracycline chemotherapy and thoracic radiotherapy [5–7]. Having this obesity-ALL-chemoradiotherapy triad will lead to more profound cardiometabolic morbidities in survivors [8–11]. The treatment and prevention of obesity may improve short- and long-term cardiometabolic outcomes in survivors and this needs detailed study. This systematic review aimed to assess current evidence for bariatric interventions to manage obesity in children with ALL.

2 Research question

In pediatric ALL patients, are bariatric interventions including lifestyle, medical, and surgical approaches effective in managing obesity?

3 Methods

The protocol for this systematic review has previously been published [12], and a brief description of the methodology used in its conduct is described below. This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42016051031). This review is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Table S1).

3.1 Eligibility criteria

This systematic review included studies that have reported on boys and girls less than 18 years of age who are diagnosed with all subtypes of ALL. For reports aggregating the data of ALL participants with other cancers, we extracted the specific data of ALL subjects when available. Otherwise, we contacted the Principal Investigators to request the ALL-specific data, and studies were excluded if the data could not be retrieved.

This review aimed to identify interventions in ALL patients intended for weight loss or maintenance. Bariatric medical therapies included lifestyle-based interventions implementing exercise and nutrition-based counseling approaches, and medication-based interventions using pharmacotherapeutic agents. Bariatric surgery interventions included the assessment of the use of sleeve gastrectomy, Roux-en-Y gastric bypass, duodenal switch with biliopancreatic diversion, and laparoscopic adjustable gastric banding [13].

3.2 Search strategy

A Senior Health Sciences Librarian with expertise in systematic review methodology assisted in the formulation of the search strategy. The search strategy for MEDLINE was published in the protocol paper [12]. Additional databases that were searched included CINAHL, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, and SPORTDiscus. Grey literature searches were also performed in ProQuest Dissertations and Theses A&I and clinicaltrials.gov. There were no restrictions on language or publication date, and all databases were searched from inception. The search was run initially on July 28, 2016, and finally updated on March 20, 2019. We also searched the references of eligible publications to identify potential studies that fulfill the inclusion criteria of this systematic review. Review articles were excluded but their reference lists were searched to identify eligible studies. We also excluded conference proceedings, presentations, abstracts, and editorials but searched for their full publications.

3.3 Study selection

Four reviewers assigned to two-member teams performed title, abstract, and full-text screening independently in duplicate. At each screening stage, the reviewers met and discussed the rationale for their decisions and to resolve any disagreements. A third reviewer was consulted to arbitrate persistent differences.

3.4 Data abstraction

The primary outcome for this review was the change in the body mass index (BMI) *z*-score, reported as BMI standard deviation score (SDS) in some studies, from baseline to the end of the intervention or follow-up. Secondary outcomes comprised changes in body mass including BMI percentile, BMI, and weight. Adiposity measures were assessed and included the fat mass percentage (%FM), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). Cardiometabolic health evaluation included the assessment of blood pressure.

Additional measures of obesity-related comorbidities were included such as non-alcoholic fatty liver disease and obstructive sleep apnea. We also included intervention-related adverse outcomes if reported. Biomarkers of metabolic health included the assessment of dysglycemia via homeostasis model assessment-insulin resistance (HOMA-IR) and dyslipidemia including cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

3.5 Risk of bias and quality assessment

Different tools were selected to evaluate the risk of bias for each study based on the study design. Randomized controlled trials (RCTs) were evaluated using the revised tool developed by Cochrane Collaboration (RoB 2.0) [14]. The Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool was used for non-randomized studies [15]. For uncontrolled before and after studies, we used the University of Alberta Evidence-based Practice Center (UAEPC) checklist [16]. We also used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool to evaluate the overall quality of evidence and the confidence in recommending the interventions [17].

3.6 Data analysis

The meta-analysis was done separately based on study design—RCT or uncontrolled before and after studies. For each study design, we performed the analysis if two or more eligible studies measured the same outcome with similar populations and methods. Based on these criteria, the meta-analysis was done for BMI *z*-score and BMI percentile with the summary measure of mean difference (MD).

In studies that did not report means and/or standard deviations, these were estimated from reported standard errors, confidence intervals (CI), medians, or interquartile range using standardized formulae [18, 19]. In studies that reported data on graphs, the actual values were estimated using Graph digitizer software [20]. The standard deviation of the change between pre- and post-measurements was imputed using established formulae [18]. The correlation coefficient of BMI *z*-score between different time periods was used for this imputation in the ALL and non-cancer populations as well [21]. Using the best available estimates, the coefficients 0.51, 0.75, and 0.86 were used for children who received the intervention at diagnosis, at the start of maintenance therapy, and after ALL therapy, respectively [22].

Inconsistency index (I^2) was used to quantify heterogeneity across studies. The threshold to interpret I^2 was determined *a priori* [12]. If more than 10 studies were available for an outcome, publication bias was assessed by Egger's test and visual inspection of the funnel plot. Otherwise, we estimated publication bias based on relevant conference abstracts or completed registered trials without published data [23].

4 Results

4.1 Search results

The complete screening process with reasons for exclusion is reported in Fig. 1. After excluding duplicates, we identified 1119 unique records from all databases and reference lists. A total of 1042 and 51 records were excluded after title and abstract screening, respectively. The remaining 26 records were screened against the full-text papers and 16 of those were excluded. A list of articles excluded at full-text screening, with reasons, is included in Online Resource Table S2. Of the remaining 10 eligible studies, four were RCTs [24–27], five were uncontrolled before and after studies [28–32], and one was a retrospective cohort study [33]. All study designs were listed in the protocol except for the latter study. However, this study is highly relevant and given the scarcity of evidence, we decided to include it as well.

The original goal of this review was to identify interventions treating overweight or obesity in childhood survivors of ALL. However, we found only one study aimed at managing overweight or obesity in survivors [25]. The rest of the studies included patients regardless of their BMI *z*-score or BMI percentile and aimed to prevent overweight or obesity [24, 26–33]. In addition, the majority of studies administered the interventions before the ALL treatment ended [24, 26–28, 30, 32, 33]. As early interventions to prevent overweight or obesity have been greatly valued [34, 35], we decided to include any patients diagnosed with ALL, regardless of their weight status and treatment stage. Additionally, the study by Hartman et al was focused on the delivery of an exercise intervention to maintain bone mineral density during ALL treatment. We ended up including this study as BMI measures and DXA scans to measure adiposity changes were assessed during the trial [24].

4.2 Lifestyle intervention

Although we included search terms for pharmacotherapy and bariatric surgery, all the identified studies involved the implementation of lifestyle interventions to manage overweight and obesity. The study characteristics and results are summarized in Table 1.

Lifestyle interventions were also administered when patients were under this age, except for one study that recruited those who were 16–30 years old at the time of participation [29]. In particular, four studies focused on young children age 4–10 years [27, 28, 30, 32] and another one recruited children 6–14 years of age [31]. There were 54 female and 93 male participants in these studies. The duration of the interventions ranged from 3 to 24 months. Three studies reported the ethnicity of participants [25, 26, 33]. Sixty-nine out of 127 participants (54%) were of Hispanic ethnicity. Only one study examined ethnicity in the analysis and concluded that it was not a significant predictor for BMI *z*-score during maintenance therapy [33].

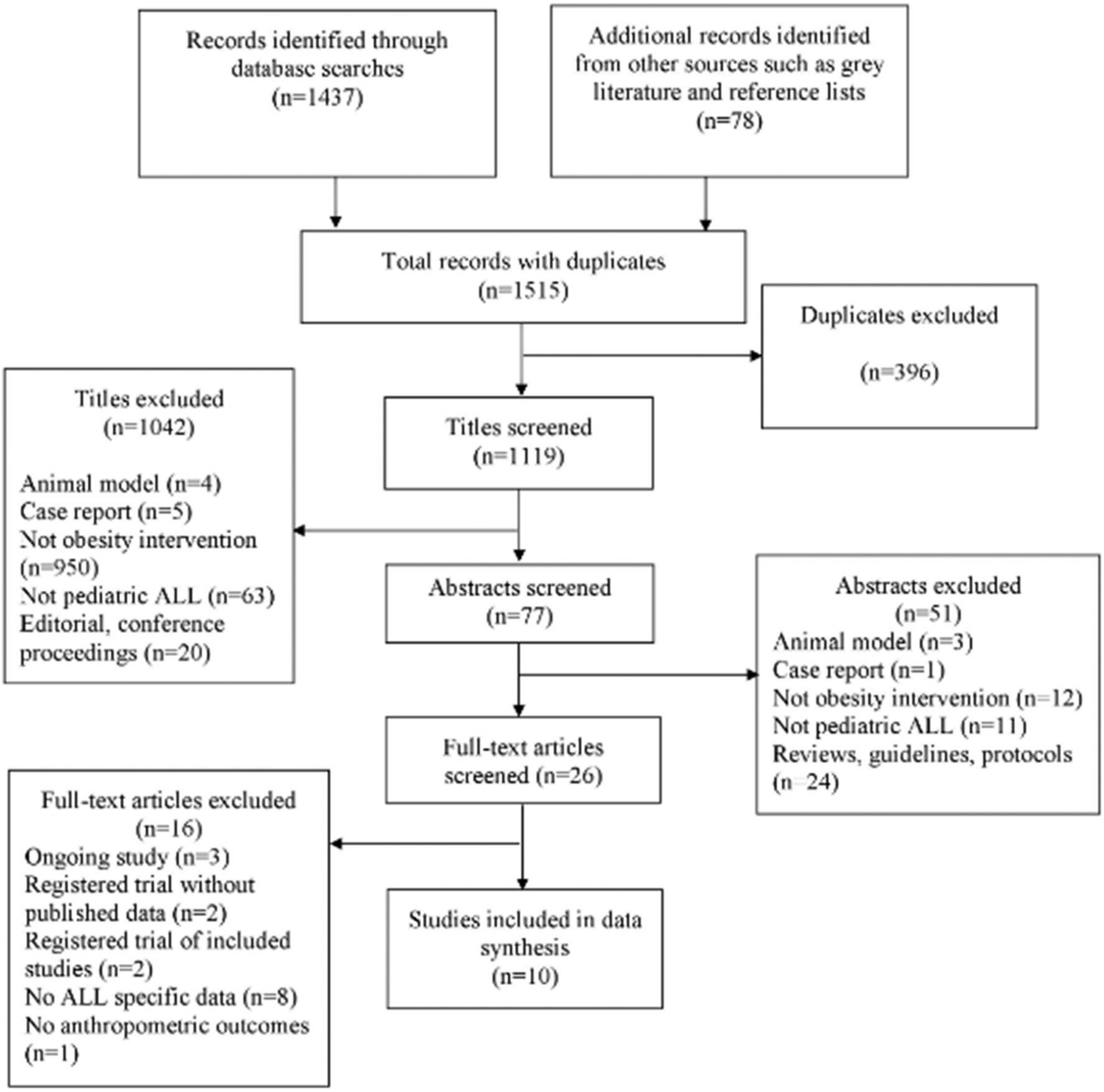

Fig. 1 Flow diagram of article screening process

Significant variation was noted in the obesity intervention design. One study provided dietary consultation only [26], while five studies prescribed specific exercises for the patients to perform at home, hospital, or a local clinic without dietary recommendations [24, 28–31]. The other four studies provided a combination of diet and exercise recommendations [25, 27, 32, 33].

Studies also differed in their timing of initiation of the interventions. While one study started the lifestyle intervention at diagnosis [24], three studies recruited participants who have completed ALL treatments [25, 29, 31]. The other six studies started the lifestyle intervention during the maintenance phase of ALL therapy [26–28, 30, 32, 33].

4.3 Outcomes and effectiveness

A meta-analysis was performed for BMI *z*-score among three RCTs [24, 25, 27] and for BMI percentile among two uncontrolled before and after studies [28, 32]. The other studies were not included in the meta-analysis due to the lack of the same outcome measurements and/or different study designs [26, 30, 31]. In addition, one study was excluded from the meta-analysis because it did not provide sufficient data and imputation was not possible [33]. Another study was also excluded because it was the only study that included adult patients [29].

The pooled MD of change of the BMI *z*-score between intervention and control groups was −0.05 (95% CI −0.18, 0.08) and the MD of the BMI percentile between pre- and post- measurements was 0.28 (95% CI −8.16, 8.72) (Fig. 2). Fixed and random effects models produced exactly the same results. The results are consistent with most of other studies not included in the meta-analysis, where all did not report significant changes in BMI, BMI *z*-score, BMI percentile, and weight with the use of different lifestyle interventions. It should be

Table 1 Summary of study characteristics and results

Author, year, country	Study design	Intervention/control	Duration	Sample size (total, female), age	Outcomes	Pre[a]	Post[a]	p value[b]
At diagnosis								
Hartman et al. 2009 (Netherlands)	RCT	Exercise to maintain function, mobility, flexibility, and short-burst high-intensity exercise	Once-twice a day for 2 years PT sessions every 6 weeks	Intervention 25, 11 F[c] Median 5.3 (1.3–15.6) years	BMI *z*-score[d] %FM *z*-score[d] LBM *z*-score[d]	− 0.33 ± 1.05 0.47 ± 1.15 − 0.46 ± 0.97	1.20 ± 1.05 1.51 ± 0.79 − 1.07 ± 0.76	0.69 0.25 0.16
		Standard care for ALL treatments (referral to local PT was allowed)		Control 26, 10 F[c] Median 6.2 (1.7–17.1) years		− 0.38 ± 0.98 − 0.22 ± 1.20 − 0.66 ± 1.01	1.00 ± 1.03 1.34 ± 0.96 − 0.78 ± 0.94	
During maintenance therapy								
San Juan et al. 2007 (Spain)	Uncontrolled	Hospital-based gym with weight training machines for children (strength and aerobic exercise)	3 times per week for 4 months Each time 90–120 min	7, 3 F Mean 5.1 ± 1.2 years	Weight (kg) Biochemical blood parameters[e]	25.1 ± 5.8 nr	25.8 ± 5.9 nr	ns ns
Moyer-Mileur et al. 2009 (USA)	RCT	Intervention: personalized exercise for muscle development, flexibility, aerobic exercise + monthly nutrition educational materials	3 times per week for 12 months Each time 15–20 min	Intervention 6, 3 F Mean 7.2 ± 0.7 years	BMI *z*-score[f] Weight *z*-score[f]	0.48 ± 1.44 0.08 ± 1.59	0.65 ± 0.84 0.37 ± 0.92	ns ns
		Control: standard advice on diet and PA		Control 7, 3 F Mean 5.9 ± 0.7 years		0.35 ± 1.13 0.11 ± 1.03	0.64 ± 1.20 0.34 ± 1.17	
Wright et al. 2013 (Canada)	Uncontrolled	7 individual sessions with ALL-tailored advice to promote PA, reduce sedentary activities, and encourage healthy food and eating behaviors	7 months	12, 2 F Median 5.3 (3.9–8.5) years	BMI percentile[f]	93.3 ± 11.9	94.2 ± 10.6	0.81
Esbenshade et al. 2014 (USA)	Uncontrolled	Flexibility, strengthening, balance, and aerobic exercise + weekly counseling	6 days a week for 6 months Each workout 30–45 min	12, 2 F Mean 7.3 ± 1.8 years	BMI percentile	73.3 ± 30.5	69.2 ± 29.3	0.39
Li et al. 2017 (USA)	RCT	Monthly one-on-one client-centered counseling with dietitian + web-based cookbook	12 months	Intervention 12, 3 F 7–12 years ($n = 6$) 13–18 years ($n = 6$)	BMI BMI percentile WC (cm) Lipid profile[e] Hemoglobin A1c	28.2 ± 9.0 85.4 ± 27.1 90.4 ± 18.4 nr nr	28.8 ± 8.6 90.2 ± 15.5 88.2 ± 18.6 nr nr	0.46 1.00 0.73 nr nr
		Standard care for ALL treatments (nutrition counseling was allowed at request or referral)		Control 10, 5 F 7–12 years ($n = 6$) 13–18 years ($n = 4$)		20.4 ± 2.9 75.8 ± 17.4 71.0 ± 11.0 nr nr	21.6 ± 3.8 76.0 ± 25.6 73.8 ± 10.3 nr nr	
Hill et al. 2018 (USA)	Retrospective cohort	Main focus on nutritional education from one-on-one visits with dietitian + brief overview on exercise and behavioral change	3 visits within 6 months	Intervention 33, 13 F < 20 years (no exact value)	BMI *z*-score	0.36	0.94	< 0.001[g]
		Standard care for ALL treatments		Control 34, 16 F < 20 years (no exact value)		0.09	0.94	
Post-cancer treatment								
Takken et al. 2009 (Netherlands)	Uncontrolled		Twice a week for 3 months	4, 1 F	BMI	18.1 ± 2.7	18.4 ± 2.7	ns

Table 1 (continued)

Author, year, country	Study design	Intervention/control	Duration	Sample size (total, female), age	Outcomes	Pre[a]	Post[a]	p value[b]
		Exercise for muscle strength, aerobic, flexibility at local PT practice and at home	Each PT session 45 min	Mean 9.3 ± 3.2[h]				
Järvelä et al. 2012 (Finland)	Uncontrolled	Muscle strengthening and aerobic exercise + daily step count with pedometer + phone counseling	3–4 times a week for 4 months	17, 9 F Median 22.8 (16.9–30.3) years	BMI	25.1 ± 3.9	25.07 ± 3.9	0.87
					Weight (kg)	72.9 ± 13.9	72.89 ± 13.8	0.98
					WC (cm)	83.9 ± 11.0	82.2 ± 11.0	0.003
					WHR	0.87 ± 0.06	0.84 ± 0.06	0.002
					%FM	27.7 ± 8.3	26.8 ± 8.5	0.04
					HOMA-IR	nr	nr (decrease)	0.002
					Insulin	nr	nr (decrease)	0.01
					Glucose	nr	nr	ns
					HDL	nr	nr	ns
					LDL	nr	nr	ns
					Triglycerides	nr	nr	ns
					Systolic BP	nr	nr	ns
					Diastolic BP	nr	nr (decrease)	0.03
Huang et al. 2014 (USA)	RCT	Daily-weekly web-, text-, phone-, printed-, materials on diet, PA, behaviors tailored toward cancer survivors + phone counseling	4 months	Intervention 19, 7 F[c] Median 13 (IQR 10,16) years	BMI *z*-score	1.84 ± 0.32	1.77 ± 0.36	0.13[g]
					Weight (kg)	65.6 ± 19.5	65.5 ± 18.8	0.06[g]
					Glucose	nr	nr	0.61
					Hemoglobin A1c	nr	nr	0.86
					Triglycerides	nr	nr	0.35
					Cholesterol	nr	nr	0.60
					Systolic BP	nr	nr	0.59
					Diastolic BP	nr	nr	0.70
		Monthly printed materials on diet, PA, behaviors for healthy youth + phone counseling		Control 19, 8 F[c] Median 13 (IQR 10,16) years		2.00 ± 0.41	1.99 ± 0.41	
						70.0 ± 17.6	71.4 ± 18.1	
						nr	nr	
						nr	nr	
						nr	nr	
						nr	nr	
						nr	nr	
						nr	nr	

RCT, randomized controlled trial; *PT*, physiotherapy; *F*, female; *BMI*, body mass index; *%FM*, fat mass percentage; *LBM*, lean body mass; *ns*, not significant; *PA*, physical activity; *ALL*, acute lymphoblastic leukemia; *WC*, waist circumferences; *WHR*, waist-to-hip ratio; *HOMA-IR*, homeostatic model assessment – insulin resistance; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *BP*, blood pressure; *nr*, not reported; *IQR*, interquartile range

[a] Outcomes are reported as mean ± standard deviation (SD) or just mean. Pre- and post-measurements in this table were done right before and at the end of the intervention, except for Hill et al. (2018) which involved right before the intervention to the end of the maintenance therapy

[b] In uncontrolled studies, *p* value is the changes of values (pre *vs*. post) within the group. In randomized or non-randomized controlled studies, *p* value compares the changes of values (pre *vs*. post) between intervention and control groups. All *p* values were unadjusted unless specified otherwise

[c] Some of these subjects did not complete the study or did not have the outcomes measured. They were not included in the analysis. The author did not report the sex distribution for these subjects

[d] Graph digitizer software was used to estimate standard error of mean reported in the graph and then calculated into standard deviation with formula

[e] There was no reporting of what was measured exactly

[f] Means and/or standard deviations are estimated from reported values using standardized formula

[g] *p* values were adjusted for confounding variables identified by the investigators

[h] This number was only reported for 9 recruited patients. However, only 4 of them completed the study

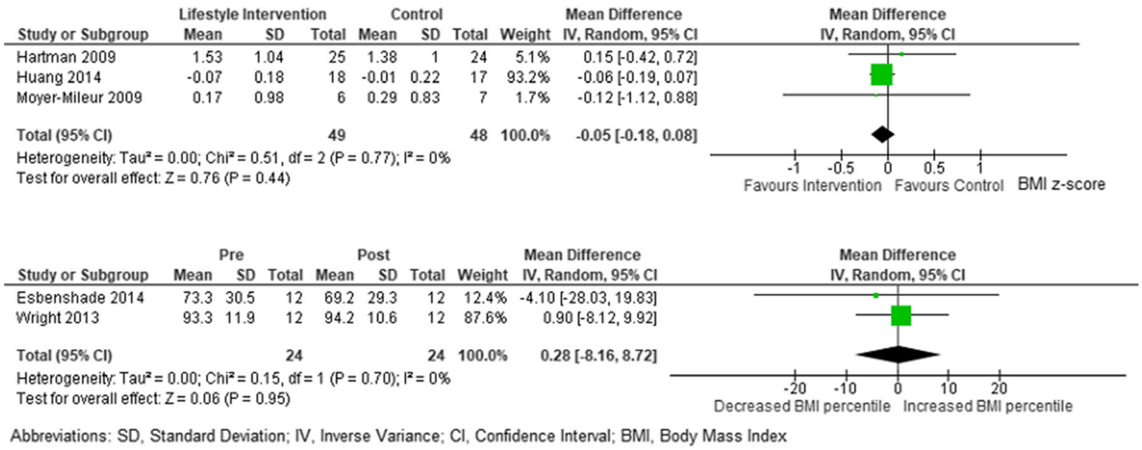

Fig. 2 Effects of lifestyle interventions on BMI z-score and BMI percentile

noted that without adjustment, one retrospective study reported the change of BMI z-score being not significant ($p = 0.08$) between the intervention and control groups [33]. However, after adjusting for the BMI z-score at diagnosis, change of BMI z-score from diagnosis to maintenance therapy, and number of months since the start of the intervention, the change of BMI z-score became significant ($p < 0.001$), favoring the intervention group. In addition, one uncontrolled study found significant changes of WC ($p = 0.003$), WHR ($p = 0.002$), and %FM ($p = 0.04$) from pre- to post-intervention measurements [29]. In contrast, changes in WC and %FM were not significant in two other studies [24, 26].

Four studies reported other outcomes such as blood pressure, glucose, insulin, hemoglobin A1c, HOMA-IR, triglycerides, cholesterol, LDL, and HDL [25, 26, 29, 30]. Two studies did not find a significant change in these outcomes with lifestyle interventions [25, 30], and one study demonstrated a significant improvement in diastolic blood pressure in supine position, fasting plasma insulin, and HOMA-IR [29]. One of the studies only described measuring hematological and biochemical blood parameters without reporting the exact measurements [30]. Another study described measuring the lipid profile and hemoglobin A1c [26]. The investigators reported no significant changes in either of these biomarker levels, but there was no information on the exact measurements. Furthermore, all studies only stated the p value for the change, but none included the exact values of these variables at baseline and after the intervention. Therefore, we could not perform a meta-analysis for the blood pressure and the biomarkers of interest.

Only two studies explicitly reported on adverse events during the study period [30, 31]. No major adverse effects were noted in one study [30], while the other study described a variety of physical symptoms during the exercise program including muscle soreness, fatigue, headache, and hyperventilation [31]. Other studies did not include a description of any adverse events related to the intervention [24–29, 32, 33].

4.4 Risk of bias and overall quality of evidence

We used the UAEPC checklist to evaluate the risk of bias for five uncontrolled before and after studies (Online Resource Table S3) [28–33]. The overall risk of bias was high in one study due to non-consecutive recruitment [29]. This study selected the participants from those enrolled in a previous study conducted by the same investigator. Two other studies also had high risk of bias due to incomplete outcomes from significant withdrawals [28, 31]. One study had a 29% dropout rate [28] while five out of nine participants (56%) did not complete the program in the other study [31]. The last two studies were judged to have low risk of bias [30, 32]. Although the outcome assessors in these two studies were most likely aware of the study purpose, its influence on height and weight measurements was likely minimal due to the objective nature of these two outcomes.

One retrospective cohort study was evaluated using the ROBINS-I tool (Online Resource Table S4) [33]. Participant selection, intervention classification and deviation, missing data, outcome measurement, and selective reporting were all rated to have low risk of bias. The overall risk of bias was moderate because confounding was expected.

Risk of bias for four RCTs was determined based on a revised tool from the Cochrane Collaboration (RoB 2.0; Online Resource Table S5) [24–27]. Two studies had some concerns for risk of bias because there was insufficient information to judge whether randomization and allocation concealment were appropriate [25, 27]. One study had high risk of bias because exchange of information about the exercise program between the intervention and the control groups was possible [24]. This study also had some missing data because of withdrawals that were related to relapse, infection, pancreatitis, and psychosis. However, dropout rates were similar between the groups.

High risk of bias was also found in another study due to the randomization process [26]. The intervention group had a significantly higher BMI and WC than the control group and outcome assessors were not blinded in this study. However, the influence on BMI was minimal and therefore judged as low risk for the outcome measurement domain. On the other hand, the influence on WC would be greater because the outcome assessor might bias the measurements knowing the intervention status for the participants.

The overall quality of evidence using GRADE was determined for BMI *z*-score and BMI percentile from studies included in meta-analysis (Online Resource Table S6). The risk of bias was determined to be serious for both outcomes. There was no heterogeneity as the $I^2 = 0$ for both outcomes (Fig. 2). However, it is important to recognize that these studies had small sample sizes ($n = 6$–25 in each group) and with a wide 95% CI. This is an implicit limitation when using this statistical method to determine heterogeneity. Nevertheless, the small sample sizes were considered for imprecision and rated to be serious for both outcomes.

Indirectness was serious for BMI *z*-score. The patients with ALL from two of the RCTs received standard advice on diet and physical activity as a control group while the intervention group received personalized advice [25, 27]. However, we aimed to compare the intervention group to standard care. Publication bias was suspected as well according to a few registered trials without corresponding publications (Online Resource Table S2). Lack of control group in the before and after studies for BMI percentile also downgraded the quality of evidence. Taken together, the overall quality of evidence reporting interventions to treat and prevent obesity in pediatric ALL using BMI *z*-score and BMI percentile as outcomes was very low.

5 Discussion

Over the past few decades, the 5-year survival rates of ALL patients rose exponentially to reach 90% in some settings [36–38]. A broader focus on survival and quality of life improvement is crucial in this new era and is already under way. Three-in-four survivors of childhood ALL are at risk of developing chronic diseases such as obesity, type 2 diabetes, and cardiovascular diseases [10, 39–43]. As obesity is a major driver of cardiometabolic risk, it is crucial that interventions are deployed to treat and prevent cardiovascular disease and diabetes and improve life expectancy.

Lifestyle factors that can contribute to obesity in childhood ALL survivors include sedentary behaviors with increased screen time and increased caloric intake [44, 45]. These children may also experience reduced physical activity during and after treatment due to skeletal abnormalities, neuromuscular impairment, reduced cardiopulmonary capacity, fatigue, and imbalance [46–50]. Therefore, lifestyle interventions that aim to alter obesogenic behaviors hold significant promise as a strategy to reduce, delay, or prevent cardiometabolic disorders.

This systematic review demonstrates that lifestyle interventions involving pediatric ALL patients administered at diagnosis, during therapy, or post-therapy did not lead to significant changes in BMI-related measures. However, the majority of studies had moderate-high risk of bias and the quality of evidence was rated as low.

While excessive weight gain during pediatric ALL therapy is multifactorial and is inconsistently linked to the use of corticosteroids [51–53], it often persists beyond treatment completion into adulthood [22, 54, 55]. Other risk factors for obesity include younger age at diagnosis, overweight or obesity at diagnosis, female sex, and Hispanic ethnicity [54–57]. Importantly, overweight or obesity in ALL is an important prognostic indicator for relapse risk, event-free survival, future cardiovascular disease, and mortality risk [58–60]. Therefore, early interventions are crucial to manage obesity in pediatric ALL and lower cardiometabolic risk.

A total of ten studies utilizing lifestyle interventions in children with ALL were identified in this systematic review. Importantly, we did not identify studies reporting on the use of pharmacotherapy or bariatric surgery in ALL patients; the latter intervention has been implemented in morbidly obese youth and rarely in hypothalamic tumors [61–63]. Further studies are needed to assess the use of pharmacotherapy or bariatric surgery in managing obesity in pediatric ALL.

While the majority of the interventions were of relatively short duration, most studies in this review demonstrated limited changes in weight, BMI, BMI *z*-score, or BMI percentile at the end of the lifestyle intervention in children with ALL. There are several explanations and implications for this.

Although appropriate randomization should have eliminated the effects of confounders, only four out of ten studies were RCTs and three of the RCTs had limitations with the reported randomization processes. Two studies adjusted for additional variables in their statistical analyses including age, BMI *z*-score at diagnosis, change of BMI *z*-score from diagnosis to maintenance therapy, and/or time since the start of the intervention [25, 33]. While the change in BMI *z*-score was not significant in one study [25], the other study demonstrated significant changes after adjustments [33]. Future studies should calculate sample size *a priori* and address potential confounders when designing the randomization strategies. Non-randomized studies must adjust for these variables in the analysis.

While BMI *z*-score is the most widely used clinical measure of obesity, recent evidence suggests that using the fat mass (adiposity) measures such as %FM, WC, and WHR may provide more meaningful data in relation to metabolic health, but only two studies measured these markers [24, 29]. In addition, there is a need for further assessment of alterations in glycemic and lipid profiles in this population. There were only four identified studies that reported non-significant change in metabolic biomarkers such as glucose, insulin, and lipid profiles [25, 26, 29, 30]. More studies of longer duration are needed to evaluate the effect of lifestyle intervention on body composition and metabolic outcomes.

One limitation imposed on the conclusions of this systematic review is that it is possible that the lifestyle interventions have some long-term effects that cannot be measured at the end of the intervention program, as all of them were of relatively short duration.

Only one study collected 1-year follow-up data after the end of the exercise intervention that was initiated at diagnosis [24]. During the exercise program, both intervention and control groups had a similar increase in BMI and %FM *z*-scores. While BMI and %FM *z*-scores decreased in both groups one year after the participants completed the program, the change was more pronounced in the intervention group. This suggests that the implementation of a healthy lifestyle program during treatment might continue to take effect and produce favorable results on a short-term basis. Future studies on lifestyle interventions should consider collecting longitudinal follow-up data to fully capture the effectiveness of lifestyle interventions on managing obesity in children with ALL.

Furthermore, adherence to lifestyle intervention programs can be a challenge, especially if the intervention is planned for a prolonged period of time. In one study, the exercise program in this study spans the entire ALL treatment period of 2 years. Some parents and children reported that it was challenging to remain motivated while receiving chemotherapy, and some may have had medical conditions that prevented them from full participation [24, 28, 31]. This demonstrates the importance of considering the side effects of treatments and personalizing the design of interventions to manage overweight and obesity in children with ALL to maximize engagement and success.

5.1 Strengths and limitations

This systematic review adopted a comprehensive search strategy. We searched the grey literature and reference lists of the eligible primary studies and relevant reviews.

Another strength of this review is that we used inclusive search terms for interventions. Based on current evidence, evaluating the effectiveness of pharmacotherapy or bariatric surgery in select cases on managing overweight and obesity in these children might still hold value but cannot be recommended outside of clinical trials.

This review identified a dominant use of lifestyle intervention and absence of other interventions on managing overweight and obesity in children with ALL. Future studies may consider a multimodal design with a combination of pharmacotherapy, diet, exercise, and behavioral components.

There are some limitations in this review. The included studies initiated the intervention at different stages of ALL treatment including diagnosis and maintenance therapy or after the completion of treatment. We could not perform meta-analyses for the studies based on treatment stages due to variability in study design and methods. As BMI *z*-score was the primary outcome of interest, we decided to include the three studies in the meta-analysis and evaluated the quality of evidence using GRADE. We expected this to impose concerns on inconsistency. However, there is no heterogeneity according to I^2 value, most likely due to small sample sizes across these studies so this result has to be interpreted with caution. The small sample sizes and imprecision downgraded the overall quality of evidence.

Another limitation is the lack of control groups in some studies included in this review. Without a control group, the effects of lifestyle interventions can be influenced by changes in the clinical condition of ALL and/or its treatment. In some studies with a control group, this group was provided with standard lifestyle advice for healthy children, in comparison to advice specific to children with ALL in the intervention group. When the control group received standard care, referral to physiotherapy or dietitian was allowed. Therefore, we were not able to make a direct comparison between lifestyle interventions *versus* no intervention. The advice the control group received in these studies might attenuate the measured difference between the intervention and the control groups.

Lastly, the outcome measures for body mass varied across studies including weight, BMI, BMI *z*-score, and BMI percentile. There was also insufficient information for our secondary outcomes of interest including glucose, insulin, lipid profiles, and adiposity measures to be assessed. Most of the studies did not describe whether or not they collected information on adverse events during the lifestyle intervention. This needs to be considered in future interventions.

6 Conclusions

This systematic review demonstrated the heterogeneity of lifestyle interventions deployed at different stages of pediatric ALL treatment. These interventions did not lead to significant changes in BMI-related measures. However, the evidence is of low quality and is limited by small sample size, relatively short duration of interventions and follow-up, and the dominance of uncontrolled study design.

We recommend that well-conducted RCTs with sufficient sample sizes are required to make definitive conclusions about the choice of the interventions to treat and prevent obesity in ALL. Future studies must include detailed measurements of adiposity such as %FM and clinical and radiological measures of visceral adiposity [66, 67]. When designing the interventions, the inclusion of a multicomponent intervention such as diet, physical activity, and behavioral approaches with or without pharmacotherapy may offer improved and more sustainable outcomes over more limited designs. Side effects noted while delivering the interventions must be recorded and reported. Furthermore, consideration should also be given to family- or parent-based interventions whereby the whole family or only the parents enroll in these interventions, which may offer additional benefits to the participant and their families. A personalized and multimodal intervention for children with ALL is needed, and outcomes need to be followed longitudinally to assess the sustainability of their effects on cardiometabolic health outcomes.

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Authors' contributions MCS is the guarantor. The research question was defined by MCS, KWW, SL, BE, AF, CP, and LT. The search strategy and eligibility criteria were developed by LB, SL, BE, CP, AF, KWW, EDS, JB, LT, and MCS. Title, abstract, and full text were screened by KWW, SL, BE, EDS, JB, and ANP. Data abstraction was done by KWW, SL, BE, ANP, and JB. Risk of bias and overall quality of evidence were evaluated by KWW, SL, BE, EDS, JB, ANP, and LS. LT and MCS provided methodological and statistical support. The manuscript was drafted by KWW and MCS and all authors reviewed, edited, and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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