abstract

BACKGROUND AND OBJECTIVE: Previous studies of survivors of pediatric acute lymphoblastic leukemia (ALL) have drawn heterogeneous conclusions regarding the prevalence of obesity and risk factors for developing obesity in pediatric ALL survivors. We sought to determine the prevalence of obesity in pediatric ALL survivors and examine risk factors for obesity through a systematic review and meta-analysis.

METHODS: A MEDLINE search was performed from its inception through 2013. Studies met the inclusion criteria if they (1) included at least 10 survivors of pediatric ALL; (2) assessed the prevalence or indicators of obesity; and (3) compared obesity among ALL survivors to a reference population or external control group. Extracted data included patient and treatment characteristics, study design, population used for comparison, and prevalence of obesity.

RESULTS: Forty-seven studies met the inclusion criteria. Despite significant heterogeneity among the studies (I^2 = 96%), the mean BMI z score in 1742 pediatric ALL survivors was 0.83 (95% confidence interval: 0.60–1.06), which corresponds to the 80th BMI percentile, indicating a significantly higher BMI in pediatric ALL survivors than the reference population. Subgroup analyses found a high prevalence of obesity in ALL survivors regardless of survivors’ receipt of cranial irradiation, gender, or age at diagnosis.

CONCLUSIONS: Obesity is prevalent in pediatric ALL survivors and is independent of patient- and treatment-related characteristics. Clinicians need to screen for obesity and its associated health conditions early in survivorship. Pediatrics 2014;133:e704–e715

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KEY WORDS
obesity, acute lymphoblastic leukemia, pediatric, survivors

ABBREVIATIONS
ALL—acute lymphoblastic leukemia
CI—confidence interval
CRT—cranial irradiation therapy

Dr Zhang conceptualized and designed the study, performed the systematic review and meta-analysis, and drafted the initial manuscript; Dr Kelly conceptualized and designed the study, performed the systematic review and meta-analysis, and reviewed and revised the manuscript; Drs Saltzman, Must, and Roberts conceptualized the study and reviewed and revised the manuscript; Dr Parsons conceptualized the study, coordinated the systematic review, and reviewed and revised the manuscript, and all authors approved the final manuscript as submitted.

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Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, accounting for ~25% of cancers diagnosed in children aged <20 years. More than 80% of the children diagnosed with ALL survive ≥5 years. This success has translated into a growing population of long-term survivors of pediatric ALL. However, cancer treatment is associated with late effects that substantially contribute to morbidity and mortality of the survivors.

One increasingly recognized late effect is obesity. Obesity contributes to the already elevated rate of chronic health conditions affecting pediatric ALL survivors. Although previous studies have demonstrated a high prevalence of obesity in pediatric ALL survivors, most comprised a small sample size, and the definition of obesity varied across studies. In addition, the association of obesity with various treatment and patient characteristics has been inconsistent. Some studies demonstrated an increased rate of obesity associated with cranial irradiation therapy (CRT), but others did not. With the decreasing use of CRT by cooperative groups, it remains unclear whether intrathecal and systemic chemotherapy alone are associated with obesity in pediatric ALL survivors. Female gender and a young age at diagnosis were predictors for obesity in some but not all studies. The rate of obesity may also vary by interval from cancer diagnosis. A better understanding of treatment and patient characteristics associated with obesity is needed to guide best clinical care and to inform targeted intervention.

We performed a systematic review and meta-analysis of the prevalence of obesity in pediatric ALL survivors. The primary aim of this study was to systematically evaluate whether survivors of pediatric ALL are more obese than those without cancer. A secondary aim was to explore whether the prevalence of obesity differs by receipt of CRT, gender, age at diagnosis, and interval since treatment completion.

METHODS
We followed the Preferred Reporting Items for Systematic Review and Meta-Analyses statement for reporting our results. A protocol was developed before the conduct of the systematic review and submitted to PROSPERO, an international prospective register of systematic review protocols.

Literature Search
We searched MEDLINE from inception through January 29, 2013, to identify studies that investigated obesity in ALL patients or survivors. We used medical subject heading and text words related to obesity (“obesity,” “weight,” “body composition,” “growth,” etc) in combination with survivors (“survivors,” “remission,” “disease-free survival,” etc) and ALL (“acute lymphoblastic leukemia,” “leukemia,” “precursor cell lymphoblastic leukemia-lymphoma,” etc). We consulted a research librarian in specifying the search and searched reference lists of eligible studies and relevant narrative reviews to identify additional studies that met inclusion criteria. Although we did not set any language restrictions for our MEDLINE search, we did not screen studies without abstracts available in English.

Eligibility Criteria and Study Selection
Two authors (FFZ and MK) extracted data, and each verified the other’s extracted information. Discrepancies were resolved by consensus. For each eligible study, we extracted the following information: (1) author, year, and country of publication; (2) characteristics of the study population (sample size, treatment period, age at diagnosis, age at study evaluation, years since diagnosis, and percentage receiving CRT); (3) study design (cross-sectional versus longitudinal); (4) type of control used (external control versus normative control and the source of control); (5) outcome measured (BMI,
BMI z score, BMI percentile, percentage of body fat, percentage of body fat z score, prevalence of overweight or obesity), and (6) primary findings (overall findings as well as findings by gender and by CRT when available). For those survivors who were children and adolescents at evaluation, BMI z score or BMI percentile was calculated based on age- and gender-specific BMI cutoffs of a reference population because BMI normally changes with age and varies by gender.20 The BMI z score indicates the number of SDs the measurement is away from the age- and gender-specific mean value in the reference population. A BMI z score >0 or BMI percentile >50th indicates a higher-than-average BMI.

Assessment of Study Validity/Quality Assessment

There is no standard scale to assess quality in observational non-randomized studies.21,22 To describe study-level characteristics associated with obesity in ALL survivors, we modified the Newcastle-Ottawa Scale23 and created a checklist including the following: whether the study adequately described the survivors’ ages at study evaluation, gender distribution, treatment protocols and years at diagnosis, whether the study appropriately selected the reference population or external controls, whether the study clearly defined the obesity outcome, whether the study provided the SD, SE, confidence interval (CI), or P value for the outcome, and whether the study performed subgroup comparisons by CRT and by gender. Longitudinal studies were additionally evaluated to determine if the length of follow-up was stated, and whether sample size at follow-up was provided (Supplemental Table 4).

Statistical Analysis

We performed meta-analysis for 20 studies that reported the mean BMI z score and its SD in a cohort of 1742 survivors of pediatric ALL. These survivors had completed treatment within 10 years at the time of study evaluation.8,12,15,16,24–39 Only 2 studies14,40 examined BMI z score assessed ≥10 years after the completion of treatment (ie, off treatment ≥10 years). Because neither study reported SD/SE of the BMI z score, the meta-analysis did not include survivors who were off treatment beyond 10 years.

We obtained summary BMI z scores using an inverse variance random effects model.41 For longitudinal studies, we included the outcome with the longest follow-up. Thirteen studies explicitly reported the mean BMI z score for the overall cohort. For the remaining 7 studies, the mean z score was calculated in the following ways: as a weighted average based on subgroup values (n = 5),29,33,34,37,38 estimated based on median and range (n = 1),39 or calculated based on the BMI z score at diagnosis and the change in BMI z score from diagnosis to study follow-up (n = 1).36 Ten studies explicitly reported the SD/SE of the BMI z score. For the remaining 10 studies, the SD was either calculated as a pooled SD based on subgroup values assuming equal variance (n = 5),29,33,34,37,38 calculated from the 95% CI (n = 2),16,27 estimated from median and range (n = 1),39 obtained directly from study authors (n = 1),39 or estimated based on the SD at diagnosis and SD for the change in BMI z score from diagnosis to study evaluation (n = 1).36

To explore the association between patient and treatment characteristics and obesity, we performed subgroup meta-analyses separately by receipt of CRT, gender, and interval since treatment completion. We also performed sensitivity analyses to assess the robustness of our findings. First, we performed the analysis after excluding 7 studies29,33,34,36–39 for which the mean BMI z score or its SD was not explicitly reported or could not be calculated based on subgroup values (for mean BMI z score) or 95% CIs (for SD of BMI z score). We also repeated the analysis after excluding 7 longitudinal studies that did not report sample size of survivors at the follow-up evaluation,8,12,29,33,34,36,38,42 for which we substituted it with the sample size reported at cancer diagnosis assuming loss to follow-up was random. In addition, we performed a “leave-one-out meta-analysis” to evaluate the impact of individual studies on the summary estimates.45

We assessed between-study heterogeneity by using Cochran’s Q statistic44 and the I² index.46 The Cochran’s Q statistic tests whether there is heterogeneity between the individual study estimates in a meta-analysis and follows a χ² distribution. The Cochran’s Q was considered statistically significant at P<.1. The I² index represents the proportion of between-study heterogeneity that is beyond chance, ranging between 0% and 100%. Higher values indicate greater inconsistency across studies. All analyses were conducted by using Stata version IC/12.1 (Stata Corp, College Station, TX) and OpenMeta-Analyst (http://www.cebm.brown.edu/software). Statistical significance was defined as a 2-sided P value <.05 for all tests except those for heterogeneity.

RESULTS

Included Studies

Our initial search identified 1164 studies. After screening titles and abstracts, 70 studies were considered potentially eligible and were retrieved for full text review. Of these, 29 were excluded and 41 were eligible for this systematic review. Six additional studies were identified by a search of the reference lists. As a result, the systematic review
included 47 studies reporting on 9223 pediatric ALL survivors for this systematic review (Fig 1). Tables 1, 2, and 3 summarize the characteristics of the eligible studies. The tables are divided by the length of time from completion of treatment to time at which the survivors were assessed.

**Meta-Analysis of BMI z Scores**

Twenty studies provided data for mean and SD of BMI $z$ score and were included in the meta-analysis. The overall BMI $z$ score in 1742 pediatric ALL survivors, off treatment, 10 years was 0.83 (95% CI: 0.60–1.06; Fig 2), which correspond to the 80th BMI percentile, suggesting that pediatric ALL survivors have significantly higher BMIs than children of same age and gender in the reference population. The mean BMI $z$ score of pediatric ALL survivors was also higher than the mean BMI $z$ score of children aged 8 to 18 years examined at the 1999–2004 NHANES, ranging between 0.4 and 0.6.46 However, there was substantial between-study heterogeneity ($I^2 = 96\%$; $P < 0.01$). Subgroup meta-analyses demonstrated that both survivors within 5 years from the completion of treatment (ie, off treatment $<5$ years) and those at 5 to 9 years from the completion of treatment (ie, off treatment $5–9$ years) had a significantly higher BMI $z$ score compared with reference populations; the BMI $z$ score in 1391 survivors off treatment $<5$ years was 0.89 (95% CI: 0.60–1.18), and the BMI $z$ score in 755 survivors off treatment 5 to 9 years was 0.64 (95% CI: 0.38–0.90). Survivors also had a higher than average BMI regardless of receipt of CRT or gender (Fig 3).

**Sensitivity Analysis**

Sensitivity analysis demonstrated that BMI $z$ score remained unchanged in ALL survivors after excluding studies that did not explicitly report the mean and/or SD of the BMI $z$ score (0.7, 95% CI: 0.5–1.0) or after excluding studies that did not report the sample size of survivors at the follow-up (0.8, 95% CI: 0.5–1.1). Consistent BMI $z$ scores were observed in the leave-one-out meta-analysis, ranging from 0.8 to 0.9 (Supplemental Fig 4).

**Assessment of Quality and Reporting**

All 47 studies clearly defined the obesity outcome. Most studies clearly stated survivors’ age (89.4%) and gender distribution (97.9%), treatment protocols (93.6%), and adequately described (93.8%) and appropriately selected (90.9%) the reference population or external controls for comparison. Seven of the 47 studies (14.9%) did not explicitly report the SD or did not present sufficient data to allow for the estimation of SD. Twenty-six of the 27 longitudinal studies (96.3%) described the length of follow-up, and 7 of the 26 studies (25.9%) did not provide the sample size at the follow-up. Twenty-two of the 30 studies (73.3%) that included both survivors treated with CRT and without CRT performed subgroup analysis by receipt of CRT, and 28 of the 47 studies (59.6%) performed subgroup analysis by gender (Supplemental Table 4).

**Prevalence of Obesity in Pediatric ALL Survivors**

Many studies did not report a BMI $z$ score but reported prevalence of overweight or obesity in pediatric ALL survivors (Tables 1–3). This is particularly true for survivors who were off-treatment $>10$ years, as many had reached adult age at the time of assessment. Five studies directly compared the BMI of the survivors with the external controls. These studies either reported similar ranges of BMI between survivors (24.0–27.4) and controls (23.7–27.1)7,15,47,48 or reported only slightly higher BMI in survivors than in controls (27.9 vs 26.8).6 Although different definitions were used to assess obesity, there was a consistently high prevalence of overweight/obesity in both recent and long-term survivors. The prevalence of overweight/obese survivors exceeded 40% in 11 studies that included pediatric ALL survivors off treatment $<5$ years (mean/median age = 7.3–15.2 years)27,28,32,50–51 (Table 1). The prevalence of overweight/obesity ranged between 29% to 69% in 14 studies that...
<table>
<thead>
<tr>
<th>Author, Year (Location)</th>
<th>Type of Control</th>
<th>Survivors, n (Control)</th>
<th>Years at Dx</th>
<th>Age at Study</th>
<th>% CRT</th>
<th>Major Findings</th>
<th>By Gender</th>
<th>By CRT</th>
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<td>CRT+: 0.8, CRT-: 0.9</td>
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<td>CRT+: 0.3, CRT-: 0.7</td>
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<td>1985–2004</td>
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<td>1990–2009</td>
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<td>0W: 9%, 0B: 11%</td>
<td>N/A</td>
<td>Higher in CRT+</td>
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<td>1997–2003</td>
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<td>8</td>
<td>0W: 46%</td>
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<td>2000–2007</td>
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<td>5.4</td>
<td>50.1</td>
<td>21%/18%, 0B: 8%, 0W: 13%</td>
<td>CRT+: 50%, CRT-: 44%</td>
</tr>
</tbody>
</table>

CRT+, survivors treated with CRT; CRT-, survivors treated with no CRT; CS, cross-sectional; Dx, diagnosis; F, female survivors; L, longitudinal; M, male survivors; N/A, values were not presented for subgroups; NHIS, National Center for Health Statistics; OB, obesity; OW, overweight; BFM, Berlin-Frankfurt-Münster; MRC, Medical Research Council.

*Normative controls are reference populations used to calculate BMI z score or percentile. External controls are usually age- and/or gender-matched healthy unrelated individuals unless sibling controls are indicated.

**Age at study and year since Dx are the mean or median as reported or estimated based on the reported age at diagnosis and duration of follow-up (the mean duration of treatment was estimated to be 2.5 y if not indicated by the study).

**Weighted average was calculated if values were provided separately for subgroups (e.g., M and F, survivors treated with CRT and without CRT).

*None: the study indicated no difference by subgroups, but the actual values were not reported for subgroups.

*The study reported the subgroup difference was statistically different (P < .05).
<table>
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<th>Author, Year (Location)</th>
<th>Study Design</th>
<th>Type of Control$^a$</th>
<th>Survivors, n/Control</th>
<th>Years at Dx $^b$</th>
<th>Age at Study $^c$</th>
<th>Years Since Dx $^d$</th>
<th>% CRT $^e$</th>
<th>Major Findings $^f$</th>
<th>By Gender $^g$</th>
<th>By CRT $^h$</th>
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<td>L</td>
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<td>33</td>
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<td>12.1</td>
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<td>0.6</td>
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<td>CRT+: 0.6, CRT –: 0.6</td>
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<tr>
<td>Craig et al 1999 (UK)</td>
<td>L</td>
<td>Normative (British)</td>
<td>213</td>
<td>1971–1994</td>
<td>17.0</td>
<td>13.8</td>
<td>100</td>
<td>0.4</td>
<td>M: 0.2, F: 0.6</td>
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<td>Normative (British)</td>
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<td>1981–1990</td>
<td>14.2</td>
<td>8.9</td>
<td>64.1</td>
<td>1.5</td>
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<td>L</td>
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<td>126</td>
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<td>18.3</td>
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<td>70.0</td>
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<td>M: 0.5, F: 0.5</td>
<td>CRT+: 0.7, CRT –: 0.04</td>
</tr>
<tr>
<td>van der Sluis et al 2000 (Netherlands)</td>
<td>CS</td>
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<td>25</td>
<td>1984–1988</td>
<td>17.2</td>
<td>11.8</td>
<td>0</td>
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<td>M: 0.6, F: 0.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Warner et al 2002 (UK)</td>
<td>CS</td>
<td>Normative (British) and external (sibling)</td>
<td>35/31</td>
<td>1979–1980</td>
<td>12.1</td>
<td>9.1</td>
<td>100</td>
<td>1.3</td>
<td>M: 0.3, F: 1.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Birkebaek et al 2006 (Brazil)</td>
<td>CS</td>
<td>Normative (British) and external</td>
<td>27/17</td>
<td>2002–2003</td>
<td>14.0</td>
<td>8.5</td>
<td>66.7</td>
<td>0.6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Craig et al 1999 (UK)</td>
<td>L</td>
<td>Normative (British)</td>
<td>213</td>
<td>1971–1994</td>
<td>17.0</td>
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<td>100</td>
<td>0.4</td>
<td>M: 0.2, F: 0.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Mayer et al 2000 (Germany)</td>
<td>L</td>
<td>Normative (British)</td>
<td>39</td>
<td>1981–1990</td>
<td>14.2</td>
<td>8.9</td>
<td>64.1</td>
<td>1.5</td>
<td>N/A</td>
<td>CRT+: 1.9, CRT –: 0.9</td>
</tr>
<tr>
<td>van der Sluis et al 2000 (Netherlands)</td>
<td>CS</td>
<td>Normative (British)</td>
<td>25</td>
<td>1984–1988</td>
<td>17.2</td>
<td>11.8</td>
<td>0</td>
<td>0.5</td>
<td>M: 0.6, F: 0.5</td>
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<tr>
<td>Warner et al 2002 (UK)</td>
<td>CS</td>
<td>Normative (British) and external (sibling)</td>
<td>35/31</td>
<td>1979–1980</td>
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<td>9.1</td>
<td>100</td>
<td>1.3</td>
<td>M: 0.3, F: 1.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**BMI z score**

<table>
<thead>
<tr>
<th>Author, Year (Location)</th>
<th>Study Design</th>
<th>Type of Control$^a$</th>
<th>Survivors, n/Control</th>
<th>Years at Dx $^b$</th>
<th>Age at Study $^c$</th>
<th>Years Since Dx $^d$</th>
<th>% CRT $^e$</th>
<th>Major Findings $^f$</th>
<th>By Gender $^g$</th>
<th>By CRT $^h$</th>
</tr>
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<tbody>
<tr>
<td>Birkebaek et al 1998 (Denmark)</td>
<td>L</td>
<td>Normative (French)</td>
<td>33</td>
<td>1973–1984</td>
<td>16.4</td>
<td>12.1</td>
<td>66.7</td>
<td>0.6</td>
<td>N/A</td>
<td>CRT+: 0.6, CRT –: 0.6</td>
</tr>
<tr>
<td>Craig et al 1999 (UK)</td>
<td>L</td>
<td>Normative (British)</td>
<td>213</td>
<td>1971–1994</td>
<td>17.0</td>
<td>13.8</td>
<td>100</td>
<td>0.4</td>
<td>M: 0.2, F: 0.6</td>
<td>N/A</td>
</tr>
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<td>L</td>
<td>Normative (British)</td>
<td>39</td>
<td>1981–1990</td>
<td>14.2</td>
<td>8.9</td>
<td>64.1</td>
<td>1.5</td>
<td>N/A</td>
<td>CRT+: 1.9, CRT –: 0.9</td>
</tr>
<tr>
<td>van der Sluis et al 2000 (Netherlands)</td>
<td>CS</td>
<td>Normative (British)</td>
<td>25</td>
<td>1984–1988</td>
<td>17.2</td>
<td>11.8</td>
<td>0</td>
<td>0.5</td>
<td>M: 0.6, F: 0.5</td>
<td>N/A</td>
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</table>

**BMI percentile**

<table>
<thead>
<tr>
<th>Author, Year (Location)</th>
<th>Study Design</th>
<th>Type of Control$^a$</th>
<th>Survivors, n/Control</th>
<th>Years at Dx $^b$</th>
<th>Age at Study $^c$</th>
<th>Years Since Dx $^d$</th>
<th>% CRT $^e$</th>
<th>Major Findings $^f$</th>
<th>By Gender $^g$</th>
<th>By CRT $^h$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkebaek et al 1998 (Denmark)</td>
<td>L</td>
<td>Normative (French)</td>
<td>33</td>
<td>1973–1984</td>
<td>16.4</td>
<td>12.1</td>
<td>66.7</td>
<td>0.6</td>
<td>N/A</td>
<td>CRT+: 0.6, CRT –: 0.6</td>
</tr>
<tr>
<td>Craig et al 1999 (UK)</td>
<td>L</td>
<td>Normative (British)</td>
<td>213</td>
<td>1971–1994</td>
<td>17.0</td>
<td>13.8</td>
<td>100</td>
<td>0.4</td>
<td>M: 0.2, F: 0.6</td>
<td>N/A</td>
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<tr>
<td>Mayer et al 2000 (Germany)</td>
<td>L</td>
<td>Normative (British)</td>
<td>39</td>
<td>1981–1990</td>
<td>14.2</td>
<td>8.9</td>
<td>64.1</td>
<td>1.5</td>
<td>N/A</td>
<td>CRT+: 1.9, CRT –: 0.9</td>
</tr>
<tr>
<td>van der Sluis et al 2000 (Netherlands)</td>
<td>CS</td>
<td>Normative (British)</td>
<td>25</td>
<td>1984–1988</td>
<td>17.2</td>
<td>11.8</td>
<td>0</td>
<td>0.5</td>
<td>M: 0.6, F: 0.5</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**% fat**

<table>
<thead>
<tr>
<th>Author, Year (Location)</th>
<th>Study Design</th>
<th>Type of Control$^a$</th>
<th>Survivors, n/Control</th>
<th>Years at Dx $^b$</th>
<th>Age at Study $^c$</th>
<th>Years Since Dx $^d$</th>
<th>% CRT $^e$</th>
<th>Major Findings $^f$</th>
<th>By Gender $^g$</th>
<th>By CRT $^h$</th>
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<tbody>
<tr>
<td>Birkebaek et al 1998 (Denmark)</td>
<td>L</td>
<td>Normative (French)</td>
<td>33</td>
<td>1973–1984</td>
<td>16.4</td>
<td>12.1</td>
<td>66.7</td>
<td>0.6</td>
<td>N/A</td>
<td>CRT+: 0.6, CRT –: 0.6</td>
</tr>
<tr>
<td>Craig et al 1999 (UK)</td>
<td>L</td>
<td>Normative (British)</td>
<td>213</td>
<td>1971–1994</td>
<td>17.0</td>
<td>13.8</td>
<td>100</td>
<td>0.4</td>
<td>M: 0.2, F: 0.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Mayer et al 2000 (Germany)</td>
<td>L</td>
<td>Normative (British)</td>
<td>39</td>
<td>1981–1990</td>
<td>14.2</td>
<td>8.9</td>
<td>64.1</td>
<td>1.5</td>
<td>N/A</td>
<td>CRT+: 1.9, CRT –: 0.9</td>
</tr>
<tr>
<td>van der Sluis et al 2000 (Netherlands)</td>
<td>CS</td>
<td>Normative (British)</td>
<td>25</td>
<td>1984–1988</td>
<td>17.2</td>
<td>11.8</td>
<td>0</td>
<td>0.5</td>
<td>M: 0.6, F: 0.5</td>
<td>N/A</td>
</tr>
</tbody>
</table>

---

$^a$ Normative controls are reference populations used to calculate BMI z score or percentile. External controls are usually age- and/or gender-matched healthy unrelated individuals unless sibling controls are indicated.

$^b$ Age at study and year since Dx are the mean or median as reported or estimated based on the reported age at diagnosis and duration of follow-up (the mean duration of treatment was estimated to be 2.5 y if not indicated by the study).

$^c$ Weighted average was calculated if values were provided separately for subgroups (eg, M and F, survivors treated with CRT and without CRT).

$^d$ None: the study indicated no difference by subgroups, but the actual values were not reported for subgroups. Yes: the study indicated a difference by subgroups, but the actual values were not reported for subgroups.

$^e$ * The study reported the subgroup difference was statistically different (p < .05).
### Table 3: Characteristics of Studies That Assessed Obesity in Pediatric ALL Survivors Off Treatment ≥10 Years

<table>
<thead>
<tr>
<th>Author, Year (Location)</th>
<th>Study Design</th>
<th>Type of Control</th>
<th>Survivors, n/Control</th>
<th>Years at Dx</th>
<th>Age at Study</th>
<th>% CRT</th>
<th>Major Findings</th>
<th>By Gender</th>
<th>By CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkebaek et al 1998 (Denmark)</td>
<td>L</td>
<td>Normative (French)</td>
<td>33</td>
<td>1973–1984</td>
<td>20.5</td>
<td>66.7</td>
<td>1.3</td>
<td>N/A</td>
<td>CRT+: 1.4, CRT−: 10</td>
</tr>
<tr>
<td>Veringa et al 2012 (Netherlands)</td>
<td>CS</td>
<td>Normative (Dutch)</td>
<td>68</td>
<td>1973–2000</td>
<td>25.0</td>
<td>45.6</td>
<td>0.5</td>
<td>M: &lt;0.1, F: 1.4</td>
<td>CRT+: 1.0, CRT−: 0.02</td>
</tr>
<tr>
<td>Brennan et al 1993 (UK)</td>
<td>CS</td>
<td>External</td>
<td>32/35</td>
<td>MRC UKALL I–X</td>
<td>1973–1984</td>
<td>23.0</td>
<td>100</td>
<td>M: 24.0, F: 24.7</td>
<td>N/A</td>
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<tr>
<td>Offinger et al 2003 (US)</td>
<td>CS</td>
<td>External (sibling)</td>
<td>1785/2565</td>
<td>1970–1986</td>
<td>24.1</td>
<td>71.1</td>
<td>0.5</td>
<td>M: 0.1, F: 1.4</td>
<td>CRT+: 1.0, CRT−: 0.02</td>
</tr>
<tr>
<td>Ness et al 2007 (US)</td>
<td>CS</td>
<td>External</td>
<td>75</td>
<td>1973–2000</td>
<td>30.2</td>
<td>66.7</td>
<td>27.4/27.1</td>
<td>N/A</td>
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<tr>
<td>Garmey et al 2008 (US)</td>
<td>CS</td>
<td>External (sibling)</td>
<td>1451/2167</td>
<td>1970–1986</td>
<td>32.3</td>
<td>25.1</td>
<td>27.9/26.8</td>
<td>N/A</td>
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<tr>
<td>Oefinger et al 2003 (US)</td>
<td>CS</td>
<td>External (sibling)</td>
<td>1785/2565</td>
<td>1970–1986</td>
<td>24.1</td>
<td>71.1</td>
<td>0.5</td>
<td>M: 0.1, F: 1.4</td>
<td>CRT+: 1.0, CRT−: 0.02</td>
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<tr>
<td>Ness et al 2007 (US)</td>
<td>CS</td>
<td>Normative</td>
<td>75</td>
<td>1970–1986</td>
<td>30.2</td>
<td>66.7</td>
<td>33.0/30.0*</td>
<td>M: 26.0, F: 38.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**BMI**

- Normative controls are reference populations used to calculate BMI z-score or percentile. External controls are usually age- and/or gender-matched healthy unrelated individuals unless sibling controls are indicated.
- Age at study and year since Dx are the mean or median as reported or estimated on the basis of the reported age at diagnosis and duration of follow-up (the mean duration of treatment was estimated to be 2.5 y if not indicated by the study).
- Weighted average was calculated if values were provided separately for subgroups (eg, M and F, survivors treated with CRT and without CRT).
- None: the study indicated no difference by subgroups, but the actual values were not reported for subgroups. Yes: the study indicated a difference by subgroups but the actual values were not reported for subgroups.
- * The study reported the subgroup difference was statistically different (P < .05).

**Gender**

- The prevalence of overweight/obesity or a higher BMI z score in male and female ALL survivors, the studies that evaluated pediatric ALL survivors off treatment 5 to 9 years (mean/median age = 13.2–14.9 years) and 10 years (mean/median age = 20.5–24.1 years), ranging from 34% to 66%.

**Major Findings**

- Consistent with the evolution of treatment protocols over time, earlier studies tended to include a higher percentage of ALL survivors treated with CRT than did recent studies. Four studies included exclusively survivors treated with CRT, and 3 studies included survivors treated without CRT. On the basis of these 14 studies, the OR for the 800 survivors treated without CRT was 0.7 (95% CI: 0.4–0.9, Fig. 2). The prevalence of overweight/obesity was fairly consistent in 5 studies that evaluated pediatric ALL survivors off treatment 10 years (mean/median age = 13.2–14.9 years) and 10 years (mean/median age = 20.5–24.1 years), ranging from 34% to 66%.

---

**Notes:**

- BMI, body mass index; CRT, chemotherapy; M, male survivors; F, female survivors; MRC, Medical Research Council; N/A, values were not presented for subgroups; OB, obesity; OW, overweight.

---

**CRIT+:** survivors treated with CRT; CRIT−: survivors treated with no CRT; CS, cross-sectional; Dx, diagnosis; %, female survivors; L, longitudinal; M, male survivors; MRC, Medical Research Council; N/A, values were not presented for subgroups; OB, obesity; OW, overweight.

---

**CRIT+:** survivors treated with CRT; CRIT−: survivors treated with no CRT; CS, cross-sectional; Dx, diagnosis; %, female survivors; L, longitudinal; M, male survivors; MRC, Medical Research Council; N/A, values were not presented for subgroups; OB, obesity; OW, overweight.

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**CRIT+:** survivors treated with CRT; CRIT−: survivors treated with no CRT; CS, cross-sectional; Dx, diagnosis; %, female survivors; L, longitudinal; M, male survivors; MRC, Medical Research Council; N/A, values were not presented for subgroups; OB, obesity; OW, overweight.
BMI z score of the 450 female survivors was 1.0 (95% CI: 0.7–1.4) and the BMI z score of the 489 male survivors was 0.7 (95% CI: 0.3–1.1; Fig 3). Among the 22 studies that assessed the prevalence of overweight/obesity by gender, 7 reported a higher prevalence of obesity in female survivors than in male survivors. However, the other 15 studies did not find evidence of a gender difference.
Chemotherapy

A few studies examined whether dose or type of glucocorticoids affected obesity. One study reported a sixfold increased risk of obesity with the highest cumulative dose of glucocorticoids, whereas 2 other studies reported no dose effects of glucocorticoids. Two studies reported a higher prevalence of obesity associated with the use of dexamethasone compared with the use of prednisone. Three studies did not observe a significant difference in obesity between the 2 glucocorticoids.

Age at Diagnosis

Eleven studies evaluated whether age at diagnosis had an impact on obesity in ALL survivors. Five studies reported a higher prevalence of obesity in association with a young age at diagnosis. It should be noted, however, that the method of defining a young age at diagnosis varied across studies. Six studies did not find an effect of age at diagnosis.

Weight Status at Diagnosis

A few studies also evaluated weight status at diagnosis, but the evidence is inadequate to warrant a conclusion. Four studies reported that being overweight/obese or having a high BMI z score at diagnosis was associated with a high prevalence of obesity. However, 1 study found a low BMI z score at diagnosis predicted obesity after treatment completion.

DISCUSSION

Although a high obesity rate has been increasingly recognized in pediatric ALL survivors, individual studies have varied appreciably by interval from cancer diagnosis and treatment protocols used for survivors. To our best knowledge, our study is the first systematic review that synthesized the literature in the past 35 years, demonstrating that obesity is prevalent in pediatric ALL survivors. The summary BMI z score in 1742 pediatric ALL survivors corresponds to the 80th BMI percentile, suggesting pediatric ALL survivors have a substantially higher BMI than the standard reference population. Our systematic review also found that obesity is prevalent in pediatric ALL survivors regardless of receipt of CRT, gender, and age at diagnosis.

The strongest evidence for an increased risk of obesity in pediatric ALL survivors came from studies that evaluated survivors who were off treatment <5 years (ie, recent survivors) and were children and preadolescents at the time of study evaluation. This was followed by studies that evaluated survivors who were off treatment 5 to 9 years and were mostly adolescents at the time of the study evaluation. A relatively smaller number of studies examined the prevalence of obesity in long-term survivors, that is, survivors who were off treatment ≥10 years. The largest study was the Childhood Cancer Survivors Study, which compared the BMI of 1451 ALL survivors to 2167 siblings and reported an overall similar BMI in survivors and siblings, although subgroup differences were also identified. Additional evidence is needed to determine whether obesity is persistent in long-term ALL survivors.

Previous studies have attributed obesity to CRT provided to patients to prevent central nervous system relapse. However, since the 1990s, central nervous system prophylaxis with CRT has gradually been replaced by intrathecal and systemic chemotherapy. Although survivors who received CRT have a slightly higher BMI z score than survivors who received chemotherapy alone, the difference is small and nearly half of the studies did not support a difference in obesity rate by receipt of CRT. In particular, for ALL survivors treated under modern protocols that do not involve CRT, a high prevalence of obesity is also observed. These results suggest that ALL survivors have an elevated risk of being overweight/obese regardless of receipt of CRT.

Corticosteroids, administered as part of the ALL treatment protocol in long-term cycles, are known to play critical roles in regulating energy intake, storage, and mobilization. Two studies examined energy intake in pediatric ALL patients on maintenance therapy and both reported a significant increase in energy intake when patients were receiving corticosteroid treatment. However, whether treatment with glucocorticoids has a long-lasting impact on obesity in pediatric ALL survivors is not known. Few studies examined the dose effect of glucocorticoids on obesity, and the current evidence is insufficient to support a link between glucocorticoids dose and obesity in ALL survivors.

Biological mechanisms that modify the risk of obesity by gender and age at diagnosis have been proposed but remain speculative. Female survivors have been found to have a higher prevalence of hyperleptinemia than male survivors, possibly due to the continuous increase in leptin and body fatness, which occurs during puberty in girls but not in boys. Genetic variations in leptin receptors have also been associated with obesity in female survivors. This systematic review suggests that female survivors may have a slightly higher BMI z score than male survivors, but the difference was small, and the overall evidence does not support a clear gender effect. The potential impact of cancer treatment on energy balance, although occurring primarily during active treatment, may last beyond the completion of treatment and become permanent. A young age at diagnosis may be a particular sensitive window for the long-lasting...
impact of treatment on energy regulation. Although a few studies suggested a young age at diagnosis is associated with a high prevalence of obesity in ALL survivors, the evidence remains inconclusive.

Limitations should be considered when interpreting our findings. Our systematic review comprised heterogeneous studies that included survivors from different countries and used different definitions to characterize obesity. Studies were also conducted over a relatively long period of time over which the treatment protocols have changed. We explored this heterogeneity with subgroup analyses and accounted for unexplained variability through random effects models. Our systematic review did not find substantial differences in BMI z scores when comparing subgroups based on patient- and treatment-related characteristics. However, it is possible that true findings between these subgroups exist but that our subgroup analyses were underpowered to detect them.

**CONCLUSIONS**

Our systematic review suggests that pediatric ALL survivors are more obese than children of the same age and gender in the reference population. The high obesity rate is observed across treatment received, gender, and age at diagnosis, although recent survivors tend to be more obese than long-term survivors. Given that ~85% of children and adolescents treated for ALL will be cured, our findings have important implications for pediatric oncologists, general pediatricians, and internal medicine/family medicine physicians, all of whom will provide long-term care to this growing population of pediatric ALL survivors. Our findings strongly suggest the need for intensive management of those who are obese, given that ALL survivors are already at increased risk of chronic health conditions. Additional research is needed to elucidate the biologic mechanisms driving the high prevalence of obesity in pediatric ALL survivors, as well as to develop and evaluate interventions targeted at preventing obesity in this at-risk population.

**ACKNOWLEDGMENTS**

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