

Trajectories of Obesity and Overweight Rates Among Survivors of Childhood Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) is the most common and survivable form of childhood cancer (Howlader et al., 2014). To date, ALL survivorship rates are greater than 90% for pediatric patients (Howlader et al., 2014), leading to a growing concern about the numerous long-term effects of childhood cancer treatment. For instance, adult survivors of childhood cancer are 8.2 times more likely to have a severe or life-threatening condition than cancer-free siblings (Oeffinger et al., 2006), and 75% of five-year childhood cancer survivors report at least one adverse health outcome (Geenen et al., 2007). Most alarming is the disproportionate impact that these adverse outcomes have by age, as a younger age at ALL diagnosis (aged 6 years or younger) is associated with worse post-treatment cardiac outcomes (Lipshultz et al., 1995; Mulrooney et al., 2009), academic achievement (Harila-Saari et al., 2007), performance/global/verbal IQ (von der Weid et al., 2003), likelihood of earning a college degree (Haupt et al., 1994; Holmqvist et al., 2010), and income as an adult (Holmqvist et al., 2010). In an effort to improve the lives and not merely the longevity of childhood ALL survivors, a need exists to identify the modifiable negative health outcomes of childhood cancer therapy and how these vary by age.

One of the most common and potentially modifiable outcomes of ALL treatment is obesity/overweight status (Asner, Ammann, Ozsahin, Beck-Popovic, & von der Weid, 2008; Oeffinger et al., 2003; Reilly et al., 2000). Numerous samples of childhood ALL survivors demonstrate obesity rates two times greater than the general population or other comparable cohorts (i.e., siblings) (Asner et al., 2008; Garmey et al., 2008; Oeffinger et al., 2003). This elevated prevalence increases the vulnerability of ALL survivors to a wide range of harmful outcomes, including hypertension, type 2 diabetes, asthma, nonalcoholic fatty liver disease, gastrointestinal problems, endothelial dysfunction, and other medical and psychological comorbidities (Pulgaron,

Purpose/Objectives: To describe the trajectories of obesity/overweight rates by age group among survivors of childhood acute lymphoblastic leukemia (ALL) from diagnosis through several years post-therapy.

Design: Longitudinal, descriptive.

Setting: Hematology/oncology clinic in the southwestern United States.

Sample: 62 child and adolescent ALL survivors receiving treatment and follow-up care from 1999–2013.

Methods: Retrospective chart review of height, weight, and body mass index.

Main Research Variables: Annual obesity/overweight rates and developmental age groups.

Findings: Different trajectories of obesity/overweight rates existed among age groups. Forty-seven percent of adolescents met the Centers for Disease Control and Prevention criteria for obesity/overweight status at some point following diagnosis, compared to 68% of school-age and 73% of preschool children. Preschool children demonstrated the most rapid rate increase following diagnosis, with a particularly susceptible period in the years immediately following therapy. Obesity/overweight persistence was most characteristic of school-age children.

Conclusions: Important variations in rate and pattern of weight status trajectories exist by age group, demonstrating that children diagnosed with ALL during the preschool and school-age developmental years have the greatest vulnerability of developing obesity/overweight status.

Implications for Nursing: Obesity/overweight prevention efforts are greatly needed in children with ALL, and efforts should occur before ALL treatment completion in preschool and school-age children.

Key Words: leukemia; pediatric obesity; adolescent; child; preschool

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2013). In addition, the accumulation of obesity and its comorbidities results in a lifetime of increased medical costs and diminished quality of life (Finkelstein, Graham, & Malhotra, 2014; Kanellopoulos, Hamre, Dahl, Fossa, & Ruud, 2013). Given that obese children and

adolescents are as much as 20 times more likely to be obese in adulthood than normal weight peers (Singh, Mulder, Twisk, van Mechelen, & Chinapaw, 2008), understanding the trajectory of obesity/overweight status among ALL-treated children is imperative so that appropriate intervention timing can be identified to prevent lifelong obese/overweight status.

Studies exploring the relationship between obesity and ALL first appeared in the mid-1980s (Ladas et al., 2005; Rogers et al., 2008; Zee & Chen, 1986). However, a limited understanding remains of how obesity affects childhood ALL survivors by age in the United States. A large majority of obesity investigations among pediatric ALL survivors involve non-U.S. samples (Asner et al., 2008; Breene et al., 2011; Love et al., 2011), limiting their generalizability to U.S. children who live in a country with one of the most obese populations in the world (National Obesity Observatory, 2009, 2013). In addition, among U.S. survivor investigations, the exploration of potential age-related obesity differences is hindered because children aged 2–18 years are regularly grouped during analysis (Baillargeon et al., 2005; Chow, Pihoker, Hunt, Wilkinson, & Friedman, 2007; Gofman & Ducore, 2009). Also, some investigations have explored obesity only during the ALL treatment period (Baillargeon et al., 2005; Esbenshade et al., 2011; Withycombe et al., 2009), and others exploring obesity among survivors used patient samples diagnosed before 1990, a period when cranial radiation therapy (CRT) was commonly part of the ALL treatment regimen (Garmey et al., 2008; Oeffinger et al., 2003; Razzouk et al., 2007). Therefore, the purpose of this study was to describe the trajectories of obesity and overweight rates for different age groups among a sample of child and adolescent ALL survivors from the United States from time of diagnosis through several years post-treatment.

Methods

Design and Sample

A longitudinal, descriptive design was used to characterize the obesity and overweight rates of child and adolescent survivors of ALL. The 62 participants in this study were (a) enrolled at the time of their first diagnosis into one of two nationally funded studies from 1999–2004 (Caron et al., 2009; Hinds et al., 2007; Stenzel et al., 2010); (b) recruited from one of the sites, Texas Children's Cancer Center in Houston; (c) were aged 3–14 years at enrollment; (d) spoke English; (e) had no known cognitive or neurologic disorders; and (f) did not receive any CRT during the observation period. All participants received ALL therapy based on the Children's Oncology Group protocols, which, depending on risk type, consisted of a combination of daunomycin, vincristine, corticosteroids, asparaginase,

methotrexate, doxorubicin, cyclophosphamide, cytarabine, and mercaptopurine across three phases: induction (one month), post-induction therapy (6–8 months), and maintenance therapy (18–24 months).

Data Collection and Measures

After receiving approval from the institutional review boards of the Baylor College of Medicine and the Duke University Health System, a retrospective chart review was conducted. Annual height, weight, and body mass index (BMI) were collected from the charts of prior study participants who returned to the cancer treatment center for yearly follow-up visits, and data were collected for all available years through 2013. Demographic data were collected from prior study records and included date of birth, race, ethnicity, and gender. Participants reporting a Hispanic ethnicity were categorized as Hispanic regardless of their reported race. Non-Hispanic participants were categorized into three groups (non-Hispanic White, non-Hispanic Black, and non-Hispanic Asian).

Annual weight status (normal weight, overweight, or obese) as defined by the Centers for Disease Control and Prevention ([CDC], 2012) was the primary outcome in this study. The CDC defines overweight as a BMI-for-age and gender from the 85th to 94th percentile, and obesity as a BMI-for-age and gender at the 95th percentile or greater. Although investigations exploring the association between ALL treatment and obesity or being overweight commonly use BMI z-scores, the current authors opted to use annual weight status because the use of z-scores has been proposed to be inefficient and less interpretable than other measures (Berkey & Colditz, 2007; Cole, Faith, Pietrobelli, & Heo, 2005).

Data Analysis

Data were analyzed using SAS[®], version 9.3. Descriptive statistics and frequency distributions were used to examine characteristics of the entire sample and each age group. Based on the child's age at time of diagnosis, participants were subdivided into three age groups: (a) preschool, ages 3–5 years; (b) school age, 6–9 years; and (c) adolescent, 10 years or older. Chi-square tests and, alternatively, Fisher's exact tests were used to test for age group differences in gender, ethnicity/race, and weight status at the time of diagnosis. Two-tailed tests were performed, with the level of significance set at 0.05 for each test.

Annual weight status (normal weight, overweight, and obese) was determined by comparing each participant's BMI to the BMI percentile curves of the age- and gender-specific CDC growth charts (www.cdc.gov/growthcharts/cdc_charts.htm). Annual weight status was used to describe the trajectories of cumulative and annual obesity/overweight rates for each age group over time. Time is the years since diagnosis, which

was selected to facilitate examination of the timing of ALL treatment on weight status. Given that each age group had a different number of follow-up years, trajectories were plotted through the last year in which the majority of the group (60% or more) had BMI data to evaluate weight status over time. Both preschool and school-age children have eight years of follow-up data and adolescents have six years. Missing values were imputed by carrying forward the previous annual weight status.

Results

Sample Characteristics

Table 1 provides the sample characteristics for the 62 children and adolescents in the study. The majority of the sample was female and non-Hispanic White, and had a normal weight status at the time of diagnosis. No significant between-age group differences were detected on the gender and ethnicity/race demographic measures. The three age groups, however, differed in the rate of obesity at diagnosis ($p < 0.01$), with a higher proportion of adolescents having an obese weight status at diagnosis (29%) compared to preschool (< 1%) and school-age (16%) children.

Cumulative Obesity and Overweight Rates

Figure 1 provides the cumulative rates of obesity/overweight status following diagnosis for each age group. Sixty-eight percent of school-age and 73% of preschool children met the CDC obese/overweight criteria at some point during the follow-up period. The cumulative obesity and overweight rate was substantially lower among adolescents; only 47% met the CDC obesity/overweight criteria at some point following diagnosis.

Annual Obesity/Overweight Rates During and Following Treatment

The trajectories of annual rates of obesity/overweight by age group and how these compare to the ALL treatment period are displayed in Figure 2. One year following ALL diagnosis, all age groups demonstrated increases in obesity/overweight rates. However, preschoolers' obesity/overweight rate more than doubled to 39%—the greatest increase among all age groups. Throughout the remainder of the ALL treatment period, the age groups exhibited varied trajectories with the obesity/overweight rates increasing for school-age children and decreasing for both preschoolers and adolescents.

Table 1. Sample Characteristics

Characteristic	Total Sample (N = 62)		Preschool (n = 26)		School Age (n = 19)		Adolescent (n = 17)	
	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD
Age (years)	7.2	3.3	4.3	1	7.1	1.2	11.9	1.6
Characteristic	n	n	n	n	n	n	n	n
Gender								
Male	28	11	8	8	8	8	8	8
Female	34	15	11	11	11	11	11	11
Ethnicity/race								
Non-Hispanic White	34	16	11	11	11	11	11	11
Non-Hispanic Black	6	–	2	2	2	2	2	2
Non-Hispanic Asian	1	1	–	–	–	–	–	–
Hispanic	21	9	6	6	6	6	6	6
Weight status								
Normal weight	46	22	13	13	13	13	13	13
Overweight	8	4	3	3	3	3	3	3
Obese	8	–	3	3	3	3	3	3

Note. Age, gender, ethnicity/race, and weight status were recorded at the time of diagnosis.

Note. Overweight is body mass index (BMI)-for-age and gender from the 85th to 94th percentile; obese is BMI-for-age and gender at the 95th percentile or higher.

Age groups also varied in their pattern of annual obesity/overweight rates during the post-treatment period. Adolescents demonstrated a decreasing trend with 41% of adolescents being obese or overweight at Year 3 and 35% at Year 6. Conversely, at one year following ALL treatment, obesity/overweight rates peaked for both the school-age (68%) and preschool (46%) groups. In addition, at five years following treatment, obesity/overweight rates were 2.5 times higher for preschoolers and 2 times higher for school-age children than at the time of diagnosis.

Obesity Persistence

Figure 3 presents the obesity rate trajectories by age group. School-age children demonstrated the greatest persistence of obesity, with 42% meeting the CDC criteria for obesity at Year 4 (after completing ALL therapy) and persisting through the end of follow-up. Both preschoolers and adolescents demonstrated considerably lower rates of obesity, and adolescents had the same rate of obesity (29%) at the end of the follow-up period as at time of diagnosis.

Discussion

This study described the trajectories of obesity/overweight rates in child and adolescent ALL survivors from time of diagnosis through several years post-therapy. The findings from this study are similar to other published reports, which reveal children and

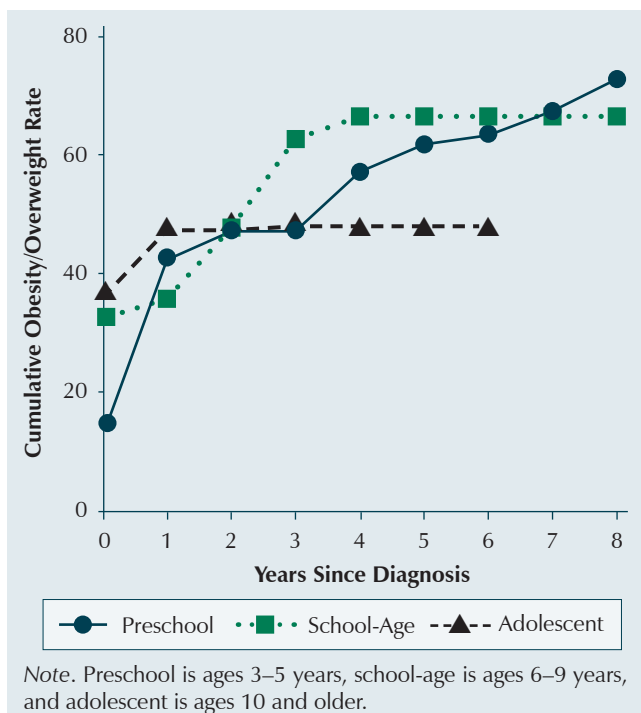


Figure 1. Cumulative Obesity/Overweight Rates by Age Group

adolescents receiving treatment for ALL have high obesity/overweight rates. However, this study demonstrates important variations in the trajectories of obesity/overweight rates by age group during and following ALL therapy.

Adolescents appear to be the least impacted by ALL treatment in terms of weight status. Although the sample of adolescents demonstrated obesity rates about 10% higher than current national trends (Ogden, Carroll, Kit, & Flegal, 2014), obesity and overweight rates marginally increased during the treatment period. In addition, at six years postdiagnosis, the obesity/overweight rate was the same as at the time of diagnosis.

In contrast, ALL survivors of the preschool age group demonstrated a particularly concerning obesity and overweight rate trajectory. Seventy-three percent of this group developed an obese/overweight status at some point in the eight years following diagnosis, which is highly significant given that many of these children were prepubescent throughout the follow-up period. Although some preschoolers had weight statuses that returned to normal weight, 39% did not. In addition, obesity/overweight prevalence peaked at one year following ALL treatment and the discontinuation of corticosteroids. Corticosteroids have been implicated for weight gain during ALL therapy (Chow et al., 2007; Jansen, Postma, Stolk, & Kamps, 2009; Murphy et al., 2006; Reilly et al., 2001), which might help explain the within-treatment obesity/overweight rate pattern

among preschoolers—increasing during higher doses of corticosteroids (e.g., induction and post-induction treatment phases) and decreasing during reduced doses (e.g., maintenance treatment phase). However, preschoolers' increasing obesity/overweight rate following ALL therapy at rates higher than survivors of the adolescent age group warrants further evaluation.

Similarly concerning are the trajectories identified for school-age children. School-age children demonstrated the highest obesity/overweight rates. Forty-two percent of school-age children were obese at four years following diagnosis and one year after treatment, a rate that is two times greater than the national prevalence among school-age children (18%) and adolescents (21%) (Ogden et al., 2014). In addition, this high prevalence persisted throughout the entire follow-up period.

The current study's results are only comparable to a few limited studies that avoided combining childhood ages during the analysis of obesity and/or BMI among children treated for ALL. Withycombe et al. (2009) explored the changes in BMI percent by age group during the course of ALL treatment, and found that preschool children (aged 2–4 years) demonstrated the lowest mean BMI percent at diagnosis, with increases across the treatment period followed by a decline during maintenance therapy. In addition, school-age children (aged 5–9 years at diagnosis) had the highest estimated mean BMI percent at the end of treatment. Both of these preschool and school age findings align with this study's within-treatment findings. However, Reilly et al. (2000) identified that Scottish children diagnosed at a younger age—particularly girls younger than age 5 years—were

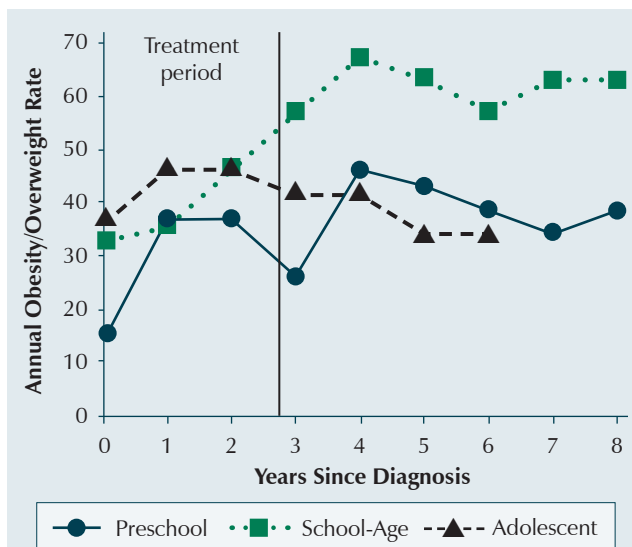


Figure 2. Annual Obesity/Overweight Rate by Age Group During and Following Treatment

at significantly greater risk of excess weight gain during treatment than older children. Why Reilly et al. (2000) found preschoolers rather than school-age children to have the greatest obesity risk during treatment is unclear, but it could be related to using a BMI measure that was independent of age and gender. Finally, among investigations exploring obesity following ALL treatment, Oeffinger et al. (2003) identified that adult childhood cancer survivors aged 0–4 years at diagnosis had the highest likelihood of obesity/overweight rates compared to survivors diagnosed at older ages; however, these age differences were explored only among children diagnosed before 1987 and treated with high doses of CRT (20 Gy or greater).

Given the limited literature exploring obesity by age among childhood ALL survivors, future investigations are critically needed to confirm the authors' descriptive findings. In addition, studies are needed to examine what factors contribute to these age-related differences in obesity/overweight prevalence. One potentially important factor warranting exploration is the age-related feeding practices of parents. Among mothers of cancer-free children, feeding style and attitudes toward feeding have been found to change as children age from preschool to school age, influencing children's weight status and eating behaviors (Faith et al., 2004; Gregory, Paxton, & Brozovic, 2010; Hendy & Williams, 2012). Investigating similar parental feeding practices and attitudes among parents of ALL-diagnosed children by the child's age will be important because "getting children to eat" frequently becomes one of the main focuses of parents during ALL treatment (Burley Moore & Beckwitt, 2004; Ladas et al., 2005). In addition, the involvement of other clinical (i.e., side effect profiles, steroid type), genetic, and environmental (i.e., parental weight status, social relationships) characteristics on these age-varying weight status trajectories also will be essential to explore.

Results of the current study need to be interpreted with caution. The small sample size and convenience sampling not only influences the generalizability of the results, but decreased the statistical power required to test for age subgroup differences in weight status across time at the 0.05 level. In addition, the authors were not able to examine the relationships between ethnicity/race, gender, and weight status. Therefore, future investigations should collect annual weight status data and conduct additional longitudinal analyses with larger samples of patients with ALL treated on current childhood cancer protocols. Similarly, collection of waist circumference and waist-to-height calculations should occur because these weight indicators are identified as better predictors of cardiovascular risk in children (Kahn, Imperatore, & Cheng, 2005).

However, these limitations should not outweigh the significant contributions of the current study. Im-

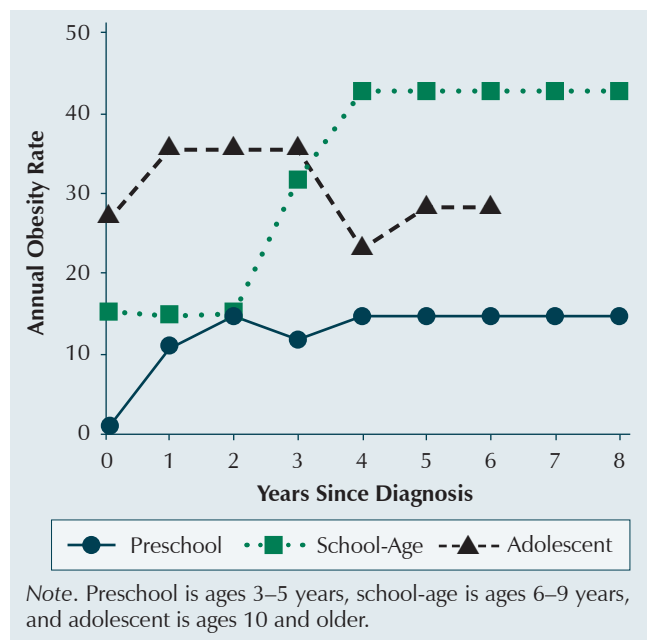


Figure 3. Annual Obesity Rate by Age Group

portant variations in weight status trajectories were identified by age group. The current study adds to the limited data that exists about U.S. childhood ALL survivors, who experience different environmental influences than children from countries with less obesity prevalence. In addition, the longitudinal nature of this study, through several years following treatment, and the use of an ALL cohort not treated by CRT, provides important updated information about the occurrence of obesity/overweight status among survivors.

Implications for Nursing Practice

This study provides important insights for oncology nursing practice, particularly regarding the timing of obesity/overweight prevention efforts. Both preschool and school-age children demonstrate a high vulnerability to sustained obesity/overweight status starting one year following ALL therapy. Although the primary focus of nutrition during ALL treatment is to prevent malnutrition and weight loss (Ladas et al., 2005, 2006; Rogers et al., 2008), the best timing for obesity prevention efforts should occur during the treatment period. However, nurses and providers should avoid initiating these efforts too early because the numerous discomforting side effects of chemotherapy that affect nutrition (e.g., nausea, altered taste, vomiting, mucositis) may cause children and parents to disregard early efforts. Therefore, similar to other preliminary intervention studies (Moyer-Mileur, Ransdell, & Bruggers, 2009), the authors suggest that nurses and clinicians consider timing obesity prevention efforts during the maintenance phase of ALL therapy when side effects reduce and

Knowledge Translation

Children and adolescents diagnosed with acute lymphoblastic leukemia (ALL) are at a disproportionate risk for obesity/overweight status.

School-age children diagnosed with ALL demonstrate the highest rates of obesity/overweight status following treatment.

Adolescents' weight status appears to be the least affected by ALL treatment.

children's appetite and energy levels have returned closer to baseline.

Conclusions

The findings from this study demonstrate that the weight status trajectories of survivors of childhood

ALL vary by age. Among the age groups, school-age children demonstrate the most concerning obesity and overweight rate trajectories with preschool children not far behind. The reasons for these age-varying trajectories are unclear, and future research exploring potential contributions will help inform the development of needed obesity prevention efforts for children diagnosed with ALL.

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