Overview of the Science: Nutritional Status, Toxicity, Outcome

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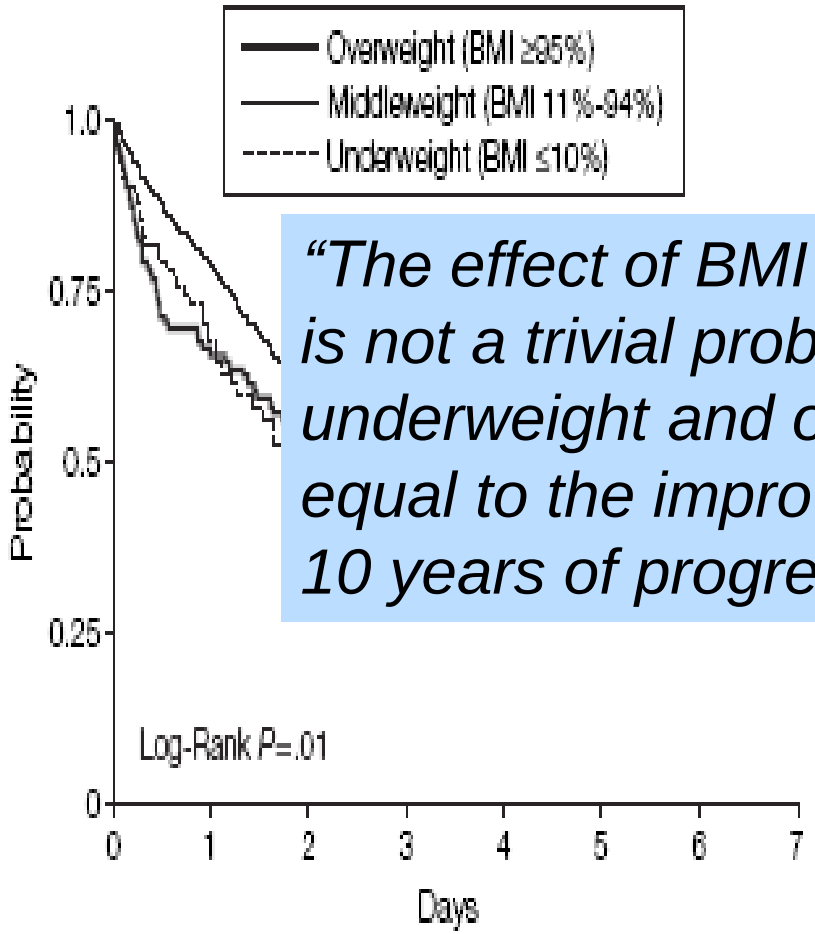
Should nutritional status be a standard part of care in pediatric oncology?



"The effect of BMI on outcome in pediatric AML is not a trivial problem: the reduced survival in underweight and overweight patients is roughly equal to the improved survival accomplished by 10 years of progress in pediatric AML."

- UW: ↓ survival (HR 1.85; 95% CI,

tality

%

ality

(HR, 3.49; 95% CI, 1.99-6.10; P= .001)

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Lange et al. JAMA 293(2):203-211. 2005. (USA)

Increased Recognition of Nutrition and Cancer

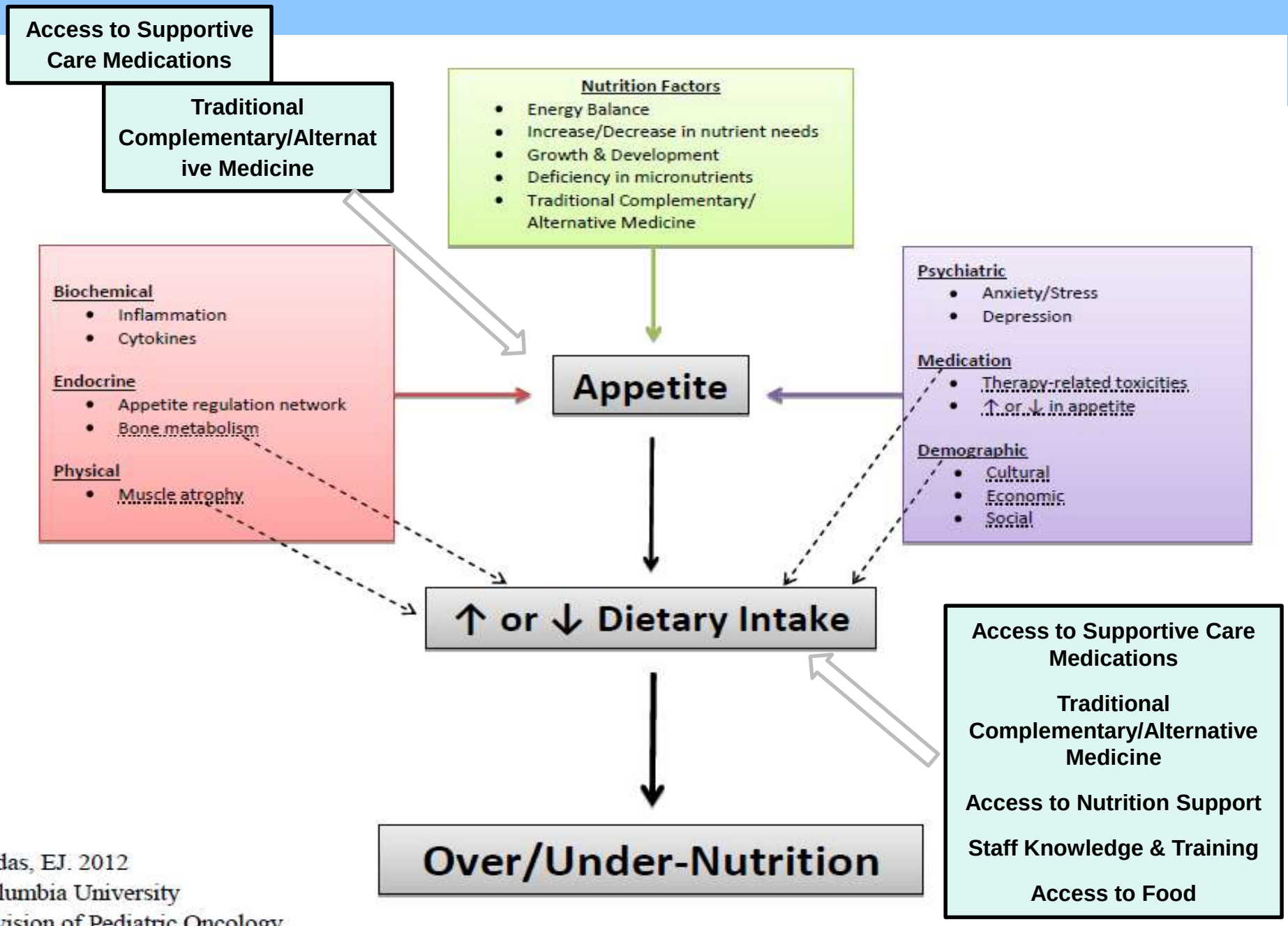
- Search terms *nutrition and oncology*

Years	# Manuscripts
1970 to 1979	11
1980 to 1989	77
1990 to 1999	285
2000 to 2010	717
2010 to 2016	1121

- Incorporated into the vision of Children's Oncology Group
  - Sung, L, Zaoutis, T, Ullrich, N, Johnston D, Dupuis, L, Ladas E. Children's Oncology Group's 2013 blueprint for research: cancer control and supportive care. Pediatr Blood Cancer. 2013 Jun;60(6):1027-30. Epub 2012 Dec 19.;
- International Society for Pediatric Oncology (SIOP)
  - In 2013, SIOP established a nutrition committee within the Pediatric Oncology Developing Countries Committee (Chairs: E Ladas, B Arora)

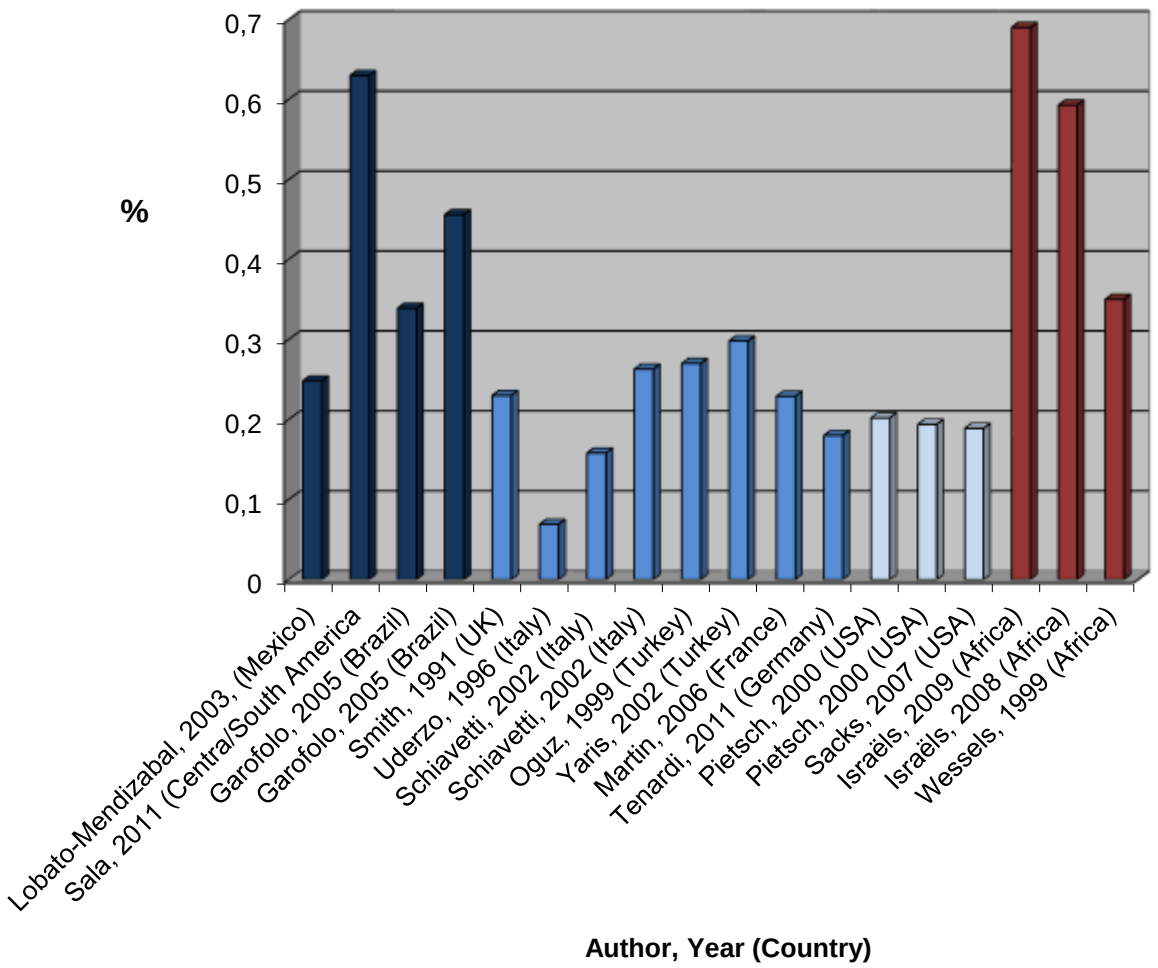
Nutrition: Definitions and Relevance

- **Categorizations of Malnutrition**
  - Undernutrition (Cachexia; Starvation)
  - Overnutrition (Obesity)
- **Clinical Importance**
  - Characterize the pattern of growth
    - Monitor changes along the growth curve and weight and height
  - Monitor the changes in the body composition as a result of altered energy intake, cancer, and cancer therapy
  - Collect prospective dietary data on patients in order to devise effective nutrition intervention protocols
- **Research**
  - Associations between malnutrition (under-/over-nutrition):
    - Increase in toxicity
    - Decreased quality of life
    - Increased mortality

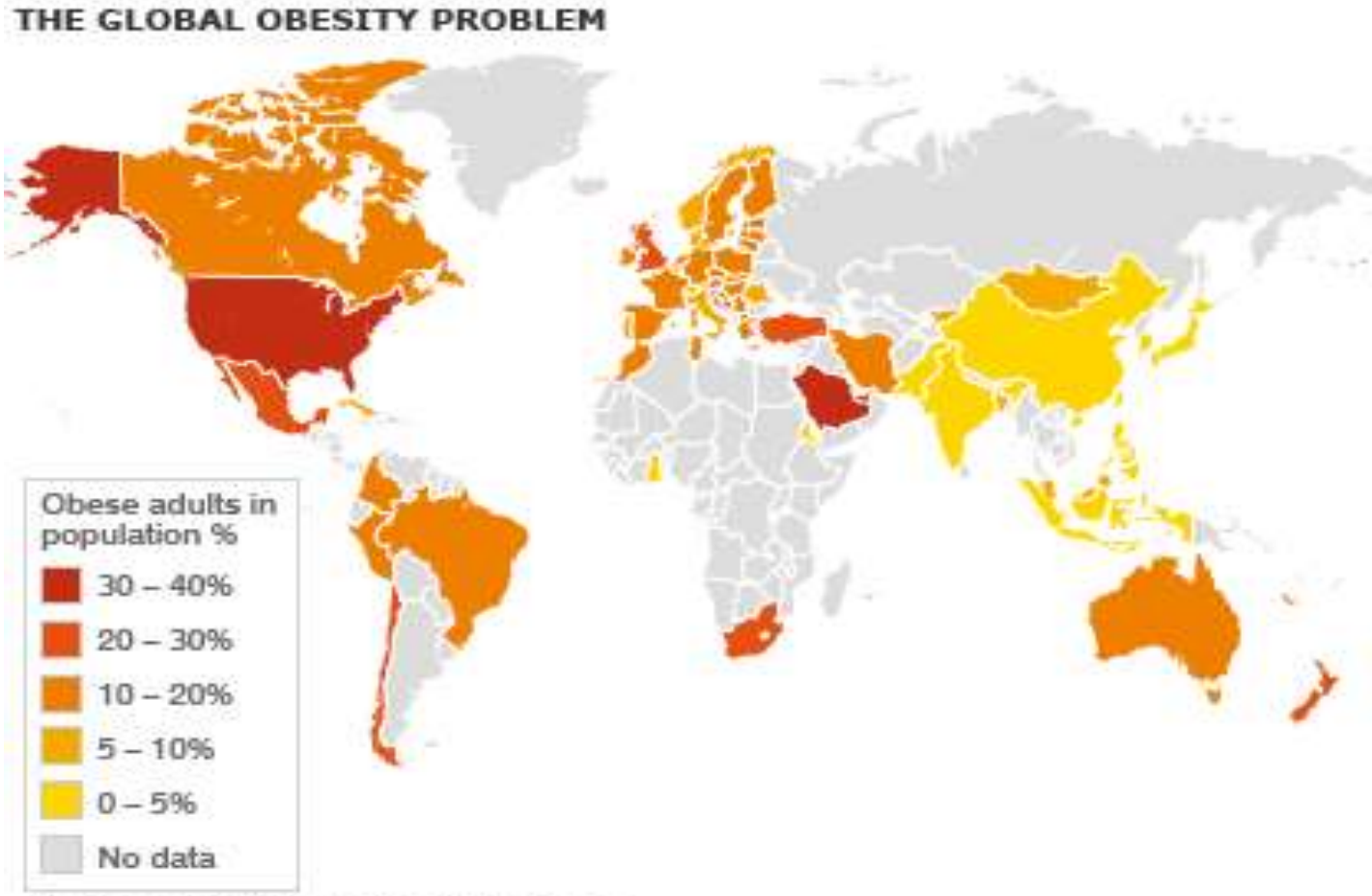


Ladas, EJ. 2012
Columbia University
Division of Pediatric Oncology

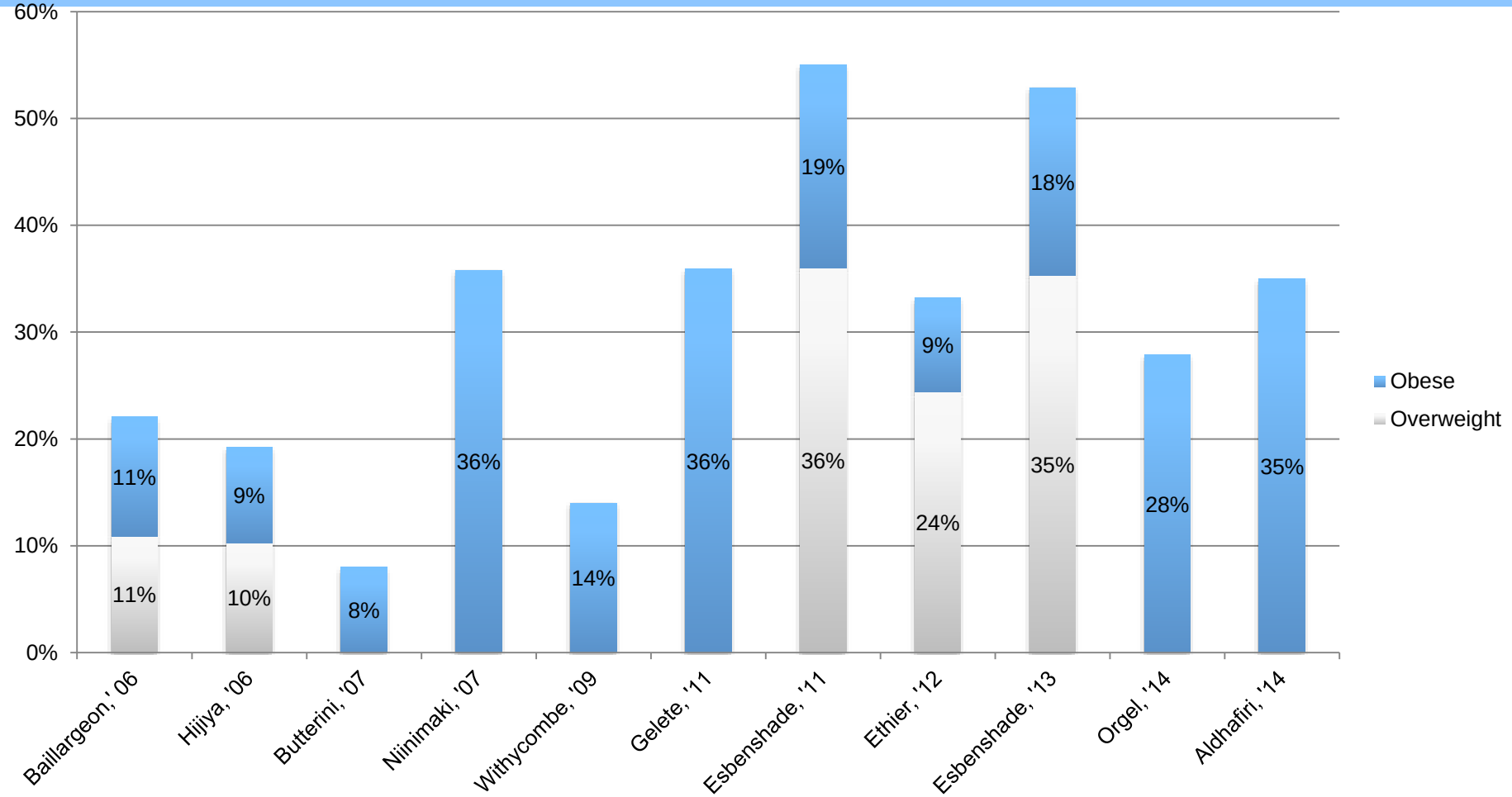
Incidence of Undernutrition at Diagnosis



However, undernutrition is only part of the story



% Overweight/Obese at Diagnosis
Acute Lymphoblastic Leukemia



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Association of body mass index and survival in pediatric leukemia: a meta-analysis[1,2]

*Etan Orgel,[3–5] Jeanine M Genkinger,[6,7] Divya Aggarwal,[8] Lillian Sung,[10] Michael Nieder,[11] and Elena J Ladas,[7–9]**

[3]Children's Center for Cancer and Blood Disease, Children's Hospital Los Angeles, Los Angeles, CA; [4]Jonathan Jaques Children's Cancer Center, Miller Children's Hospital Long Beach, Long Beach, CA; [5]Keck School of Medicine, University of Southern California, Los Angeles, CA; [6]Mailman School of Public Health, [7]Herbert Irving Comprehensive Cancer Center, [8]Institute of Human Nutrition, College of Physicians and Surgeons, and [9]Division of Pediatric Hematology/Oncology/Stem Cell Transplant, Columbia University Medical Center, New York, NY; [10]Division of Haemotology/Oncology, The Hospital for Sick Kids, Toronto, Canada; and [11]Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, FL

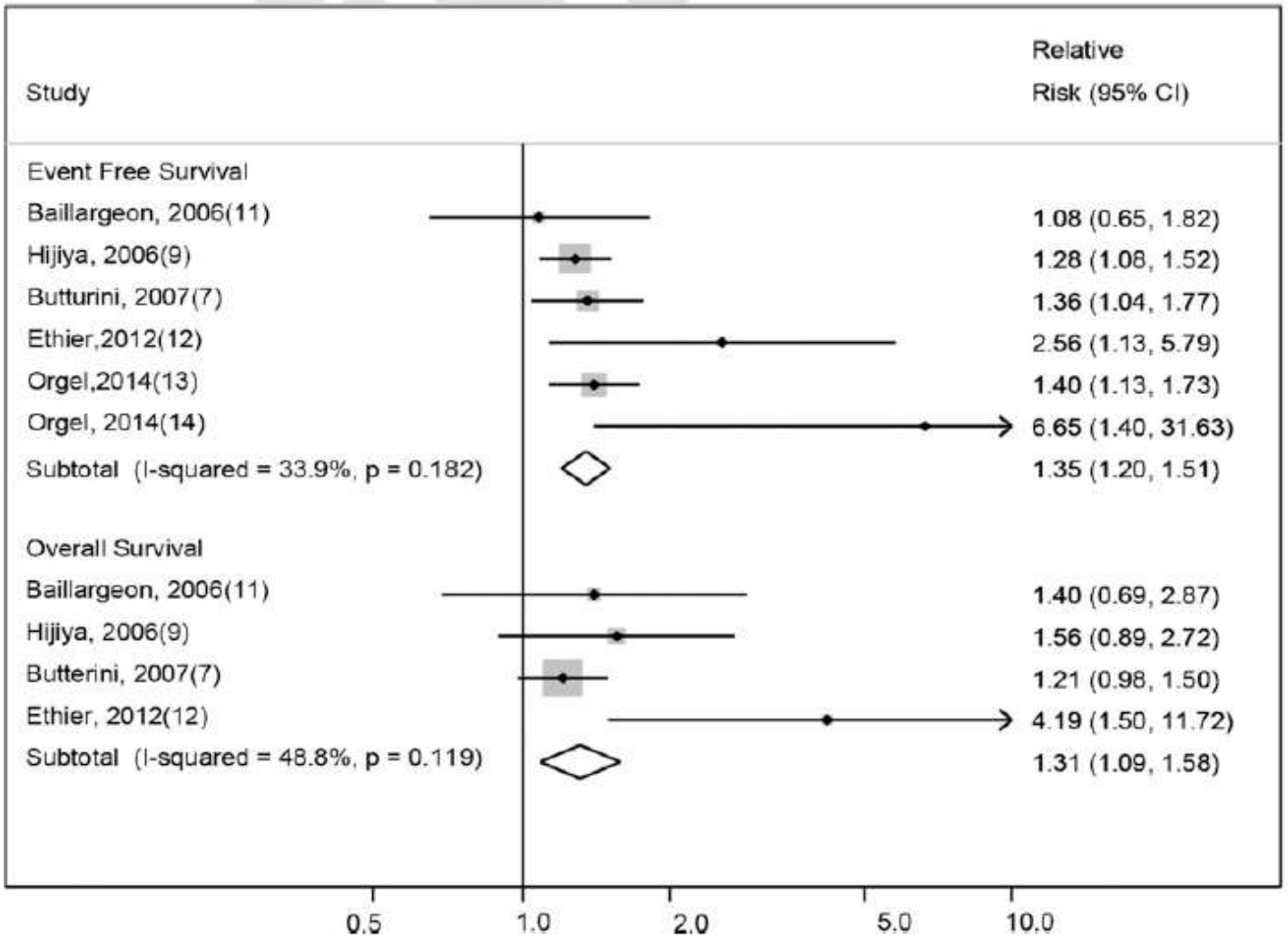
ABSTRACT

Background: Obesity is a worldwide epidemic in children and adolescents. Adult cohort studies have reported an association between higher body mass index (BMI) and increased leukemia-related mortality; whether a similar effect exists in childhood leukemia remains controversial.

Objective: We conducted a meta-analysis to determine whether a higher BMI at diagnosis of pediatric acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) is associated with worse event-free survival (EFS), overall survival (OS), and cumulative incidence of relapse (CIR).

decades (1). Acute lymphoblastic leukemia (ALL)[12] and acute myeloid leukemia (AML) constitute the 2 most common forms of childhood leukemia; together, they represent >95% of leukemia in children (0–14 y of age) and ≈90% of adolescent (15–19 y of age) leukemia (1). Epidemiologic studies frequently have used BMI to define obesity and explore its association with cancer risk and mortality (2–4). In adults, studies repeatedly have demonstrated that a higher BMI is positively associated with both the incidence of leukemia (4, 5) and leukemia-related mortality (3, 5). In children, controversy remains about whether and how childhood obesity might similarly affect leukemia

Adverse Effect of Obesity on OS and EFS in ALL



35% reduction of event free survival
(Fixed effect, RR 1.35, 95%CI 1.20, 1.51)

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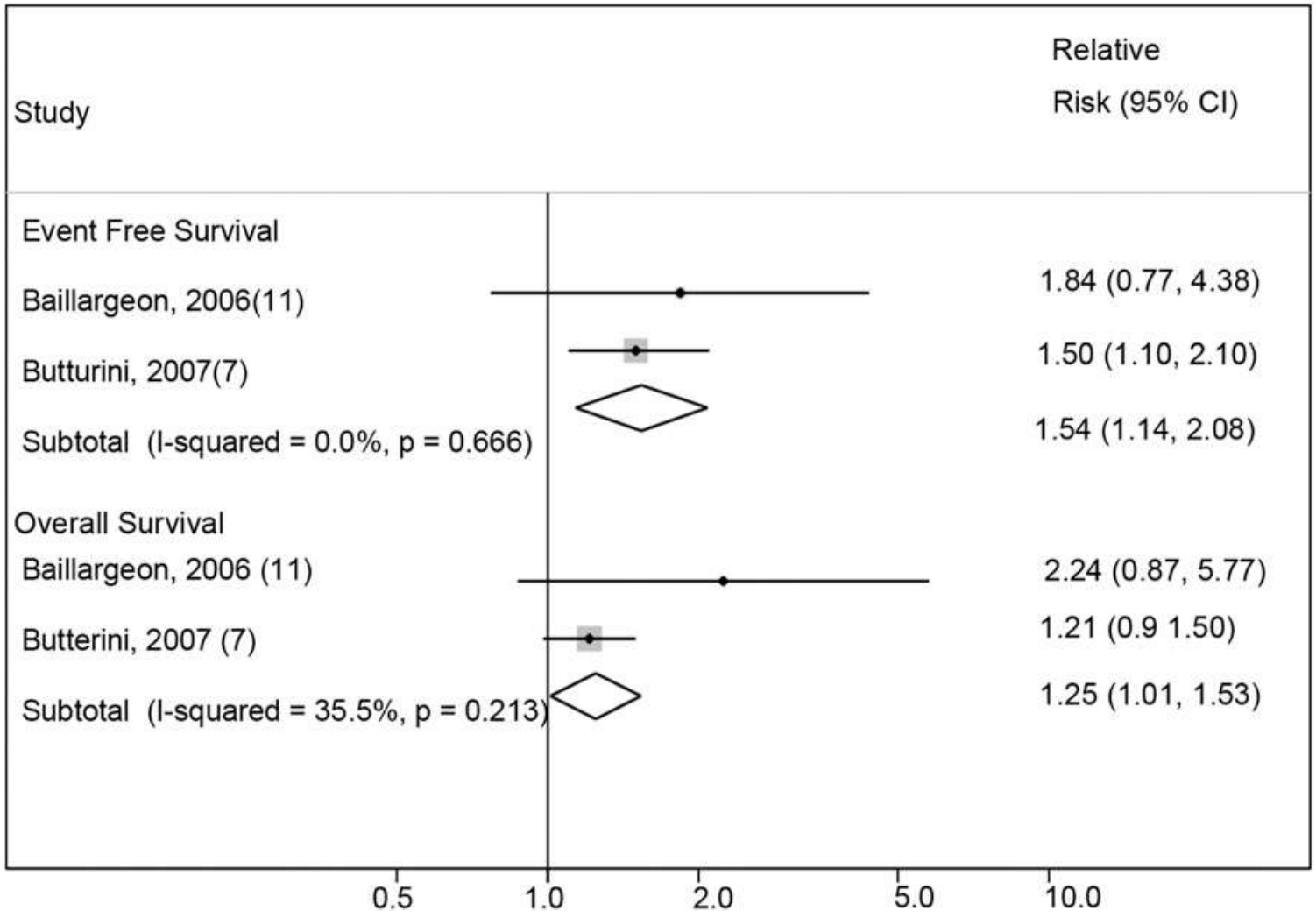
Am J Clin Nutr. 2016 Mar;103(3):808-17

A pronounced effect in adolescents



54% Increased Risk of Mortality (EFS) among older children
(Fixed effect RR: 1.54, 95% CI 1.14, 2.082)

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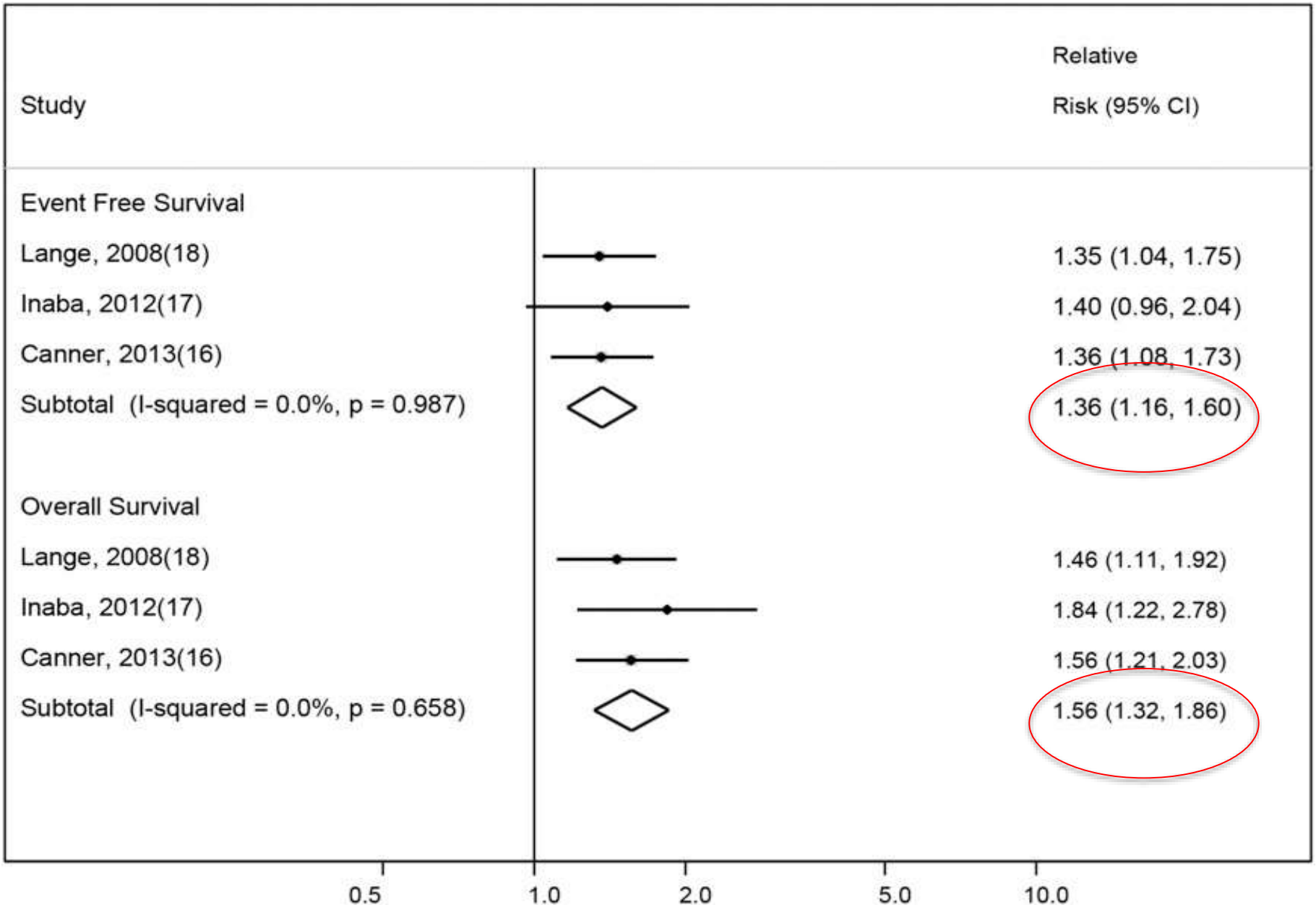
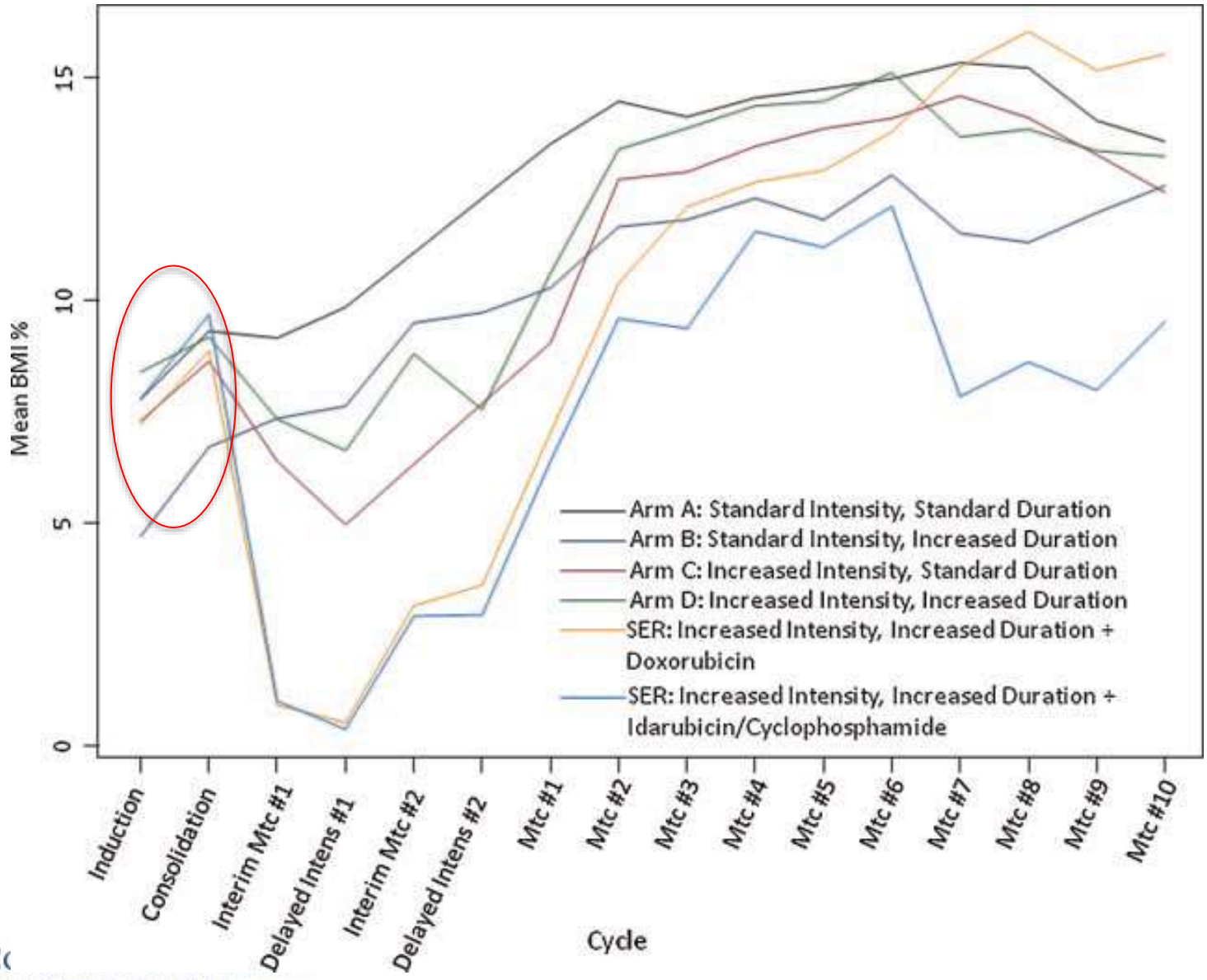
A Similar Observation in AML



Patterns of Weight Gain in ALL



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Withycomb, et al. PBC 2009; Withycomb et al PBC 2015

Early Weight Gain Predicts Weight EOT

BMI z-score at beginning of Induction				
1 unit increase	7.69	5.23	11.3	<0.0001
Difference BMI z-score during Induction				
1 unit increase	3.03	1.90	4.84	<0.0001

[illegible]	[illegible]			
BMI z-score at beginning of Induction				
1 unit increase	14.62	8.38	25.53	<0.0001
Difference BMI z-score during Induction				
1 unit increase	4.15	2.32	7.43	<0.0001

93% of patients who experienced weight gain were not overweight/obese at dx

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Withycomb et al PBC 2015

Remediation Improves Outcomes

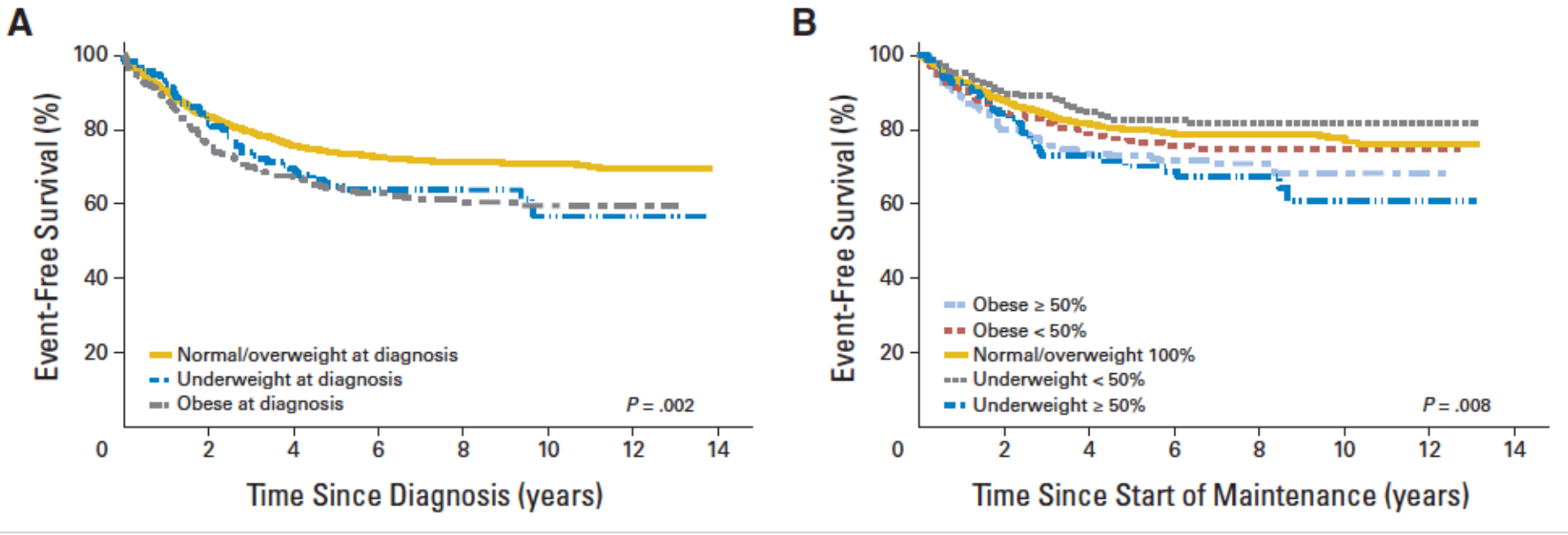

Table 2. Risk for Event by Cumulative Time at Weight Extreme Versus Weight at Diagnosis for Patients Surviving to Start of Maintenance (n = 1,581)

Weight Category at Diagnosis	Underweight ≥ 50% Time			Underweight < 50% Time			Always Normal/Overweight			Obese < 50% Time			Obese ≥ 50% Time		
	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
Underweight	33	**2.30**	**1.46 to 3.63**	60	1.09	0.68 to 1.76		—			—			—	
Normal/overweight	50	1.09	0.65 to 1.83	108	**0.52**	**0.32 to 0.83**	937	1 (referent)		146	1.04	0.74 to 1.48	42	1.51	0.95 to 2.41
Obese		—			—			—		54	0.99	0.62 to 1.58	151	**1.43**	**1.04 to 1.96**

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Orgel, et al. JCO 2014

Asociacion de Hemato-Oncologia Pediatrica de Centro America (AHOPCA)

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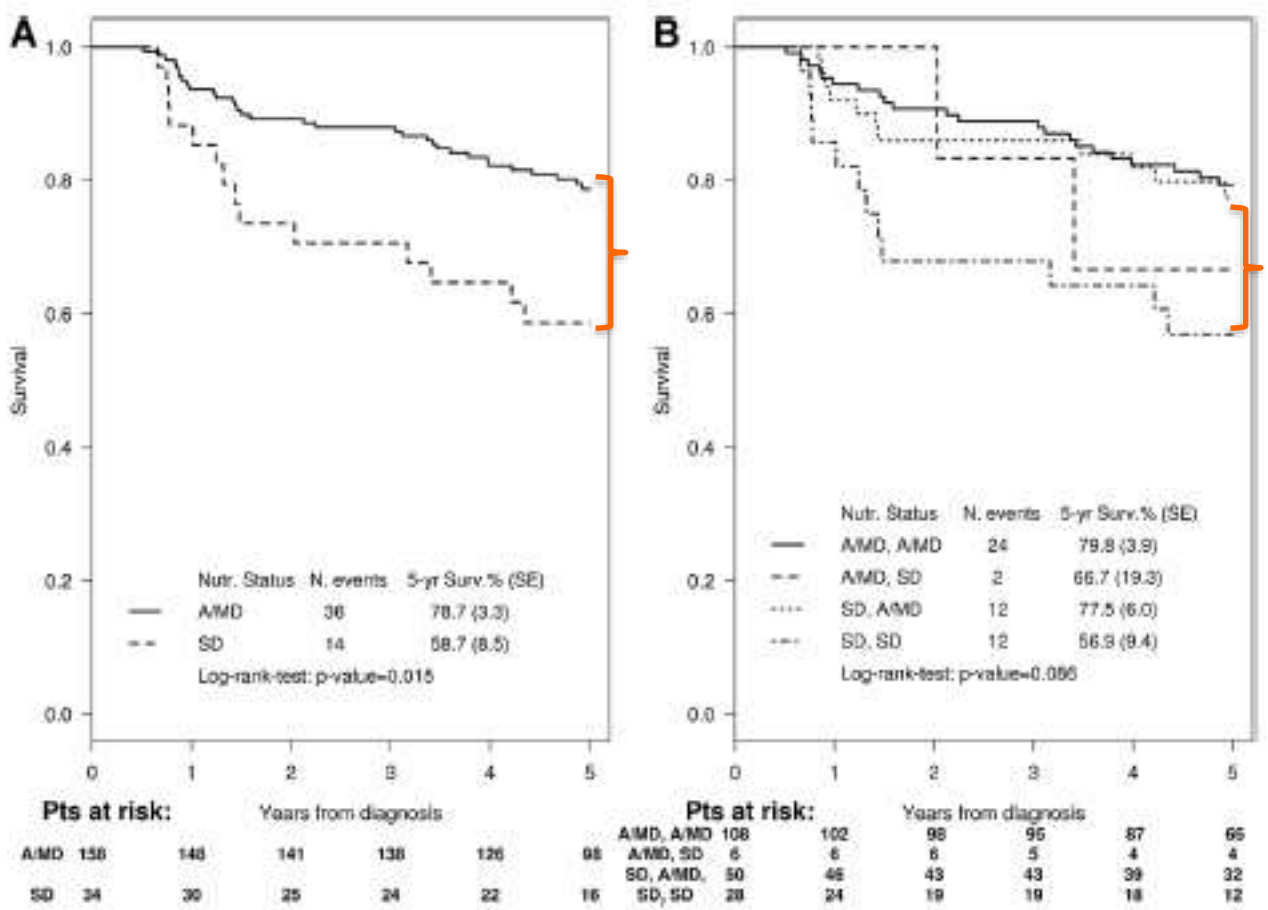
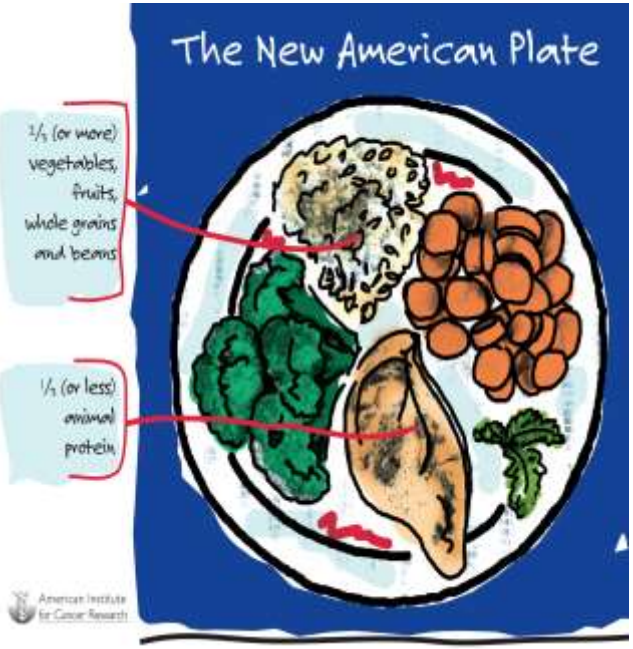


Summary of the Literature

- Nutritional status **reduces** survival, most apparent in children with ALL and AML.
  - Support for this in both HIC and LMIC
- The association of nutritional status and toxicity is less known, **more research is needed**.
- **Remediation** of undernutrition removes the risk of poor nutrition and outcome in children with cancer.
- Obesity is a clear risk factor for the **development of certain cancers**
- The effect of obesity on survival and relapse may be **underestimated**. Further research is needed.
- The effect of lifestyle variables (diet, exercise) on the development of obesity during treatment is **virtually unknown**.

What about Dietary Intake?



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Why consider diet?

- **Epidemiologic Studies**
  - Doll and Peto (1981)- Estimated nearly 70% of cancer risk is attributable to diet and exercise ; 35% of cancer risk was attributed to diet alone
    - Nurses Health Study
    - EPIC Study

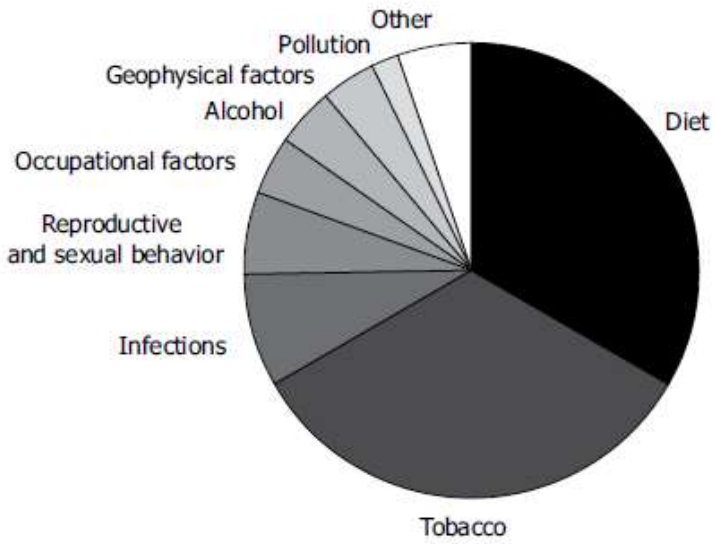

Table 1. Summary of select studies reporting on dietary intake in survivors of childhood cancer.

Author/Year	Demographics	Design	Main Dietary Findings
Badr *et al.*; 2013 [29]	N = 170/% M: 52 Mean age: 17.7 years Diagnosis: Mixed	Cross-sectional survey	96% below guidelines for fiber. 76% below guidelines for fruit and vegetables. 39% not meeting guidelines for dietary fat. Survivors who did not meet guidelines for fat intake experienced significantly ↑ general fatigue ($p = 0.04$) and cognitive fatigue ($p = 0.04$) compared to those who met guidelines. More males met guidelines for fiber ($p < 0.0001$) and fruit and vegetables ($p < 0.01$) compared to females.
Butterfield, *et al.*; 2004 [20]	N = 541/% M: 54 Mean age: 30.7 years Diagnosis: Mixed	Cross-sectional survey	68% eating more than recommended amount of red meat
Cohen *et al.*; 2012 [16]	N = 50/% M: 60 Mean age: 7.12 years Diagnosis: Mixed	Cross-sectional survey	54% of survivors exceeded estimated energy requirements by at least 110% For folate, calcium, and iron: 50%, 32%, 44% were below recommendations, respectively Most met recommendations for protein, thiamin, riboflavin, niacin, vitamin C, vitamin A, magnesium, phosphorous, and zinc
Demark-Wahnefried *et al.*; 2005 [11]	N = 209/% M: 50 Mean age: 20.3 years Diagnosis: Mixed	Cross-sectional survey	79% below guidelines for daily fruit. 68% below guidelines for calcium 84% below guidelines for dietary fat intake
Landy *et al.*; 2013 [17]	N = 91/% M: 46 Mean age: 19 years Diagnosis: Mixed	Cross-sectional survey	30% exceeded recommended values for total caloric intake; however, similar to sibling controls. ↓ total HEI scores associated with ↑ % body fat ($\beta = -0.19$, $p = 0.04$). Mean HEI score was 55.5; survivor diets moderately adherent to recommendations and dietary quality similar to siblings. Survivors exposed to cranial irradiation had lower total HEI scores (−6.4, $p = 0.01$). HEI scores were lowest for dark green and leafy greens, whole fruits, and whole grains.
Love *et al.*; 2011 [18]	N = 102/% M: 46 Mean age: 14.3 years Diagnosis: ALL	Cross-sectional survey	Normal weight survivors consumed an average of 2364 kcal/day, 315 g carbohydrate/day, 91 g protein/day, and 84 g fat/day Overweight survivors consumed an average of 2472 kcal/day, 320 g carb/day. 106 g protein/day, and 88 g fat/day
Mays *et al.*: 2012 [25]	N = 75/% M: 48 Mean age: 14.2 years Diagnosis: Mixed	Randomized, controlled trial	Survivors classified as "readiness to change" consumed significantly more milk compared to those classified as "no readiness to change" ($p < 0.001$). Survivors classified as "readiness to change" were also more likely to meet calcium recommendations ($p = 0.01$) and consume increased milligrams of calcium ($p = 0.006$).

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Ladas, Children 2014

Dietary Intake and All-Cause Mortality

	N	Death	Adherence summary score				p_{trend}
			Q1 (1.5 – 4.0)	Q2 (4.5)	Q3 (5.0 – 5.5)	Q4 (6.0 – 8.0)	
All-cause mortality							
All survivors	2,017	461	1.0	1.06 (0.81 – 1.39)	0.91 (0.72 – 1.15)	0.67 (0.49 – 0.90)	0.03
Breast cancer	938	203	1.0	0.93 (0.63 – 1.38)	0.73 (0.52 – 1.05)	0.61 (0.39 – 0.96)	0.01
Colorectal cance						.19 (0.59 – 2.43)	0.64
Gynecologic can						.96 (0.34 – 2.69)	0.94
Other cancer	437	126	1.0	1.26 (0.73 – 2.19)	1.10 (0.70 – 1.73)	0.55 (0.30 – 1.01)	0.12

33% lower all-cause mortality

Study Design: Iowa Women's Health Study
Dietary Intervention: Adherence to the AICR Guidelines
Population: Female survivors of cancer (N=2017)
Baseline Demographics: Mean age= 78.9 +/-3.9

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Inoue Choi, et al Cancer Epidemiol Biomarkers Prev . 2013 May ; 22(5): 792–802

Increase Adherence, Improved Outcome

European Prospective Investigation Into Nutrition and Cancer Cohort Study
N=378,864 males/females from 9 European countries

Causes of death	No. of cases	WCRF/AICR score categories 1	2	3	4	5	*P*-trend	HR per 1-unit increase of WCRF/AICR score
Total								
Cancer	9388	1 (reference)	0.92 (0.87, 0.98)	0.82 (0.77, 0.86)	0.80 (0.74, 0.86)	0.80 (0.69, 0.93)	<0.0001	0.91 (0.89, 0.93)
Circulatory disease	5229	1 (reference)	0.84 (0.77, 0.90)	0.73 (0.68, 0.79)	0.60 (0.54, 0.66)	0.56 (0.46, 0.69)	<0.0001	0.83 (0.81, 0.86)
Respiratory disease	1004	1 (reference)	0.82 (0.69, 0.97)	0.63 (0.53, 0.75)	0.56 (0.45, 0.70)	0.50 (0.31, 0.80)	<0.0001	0.79 (0.74, 0.85)
Other causes	4228	1 (reference)	0.84 (0.77, 0.91)	0.72 (0.66, 0.78)	0.62 (0.56, 0.70)	0.55 (0.43, 0.70)	<0.0001	0.83 (0.80, 0.86)

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Vergnaud, et al Am J Clin Nutr 2013; 97:1107-20.

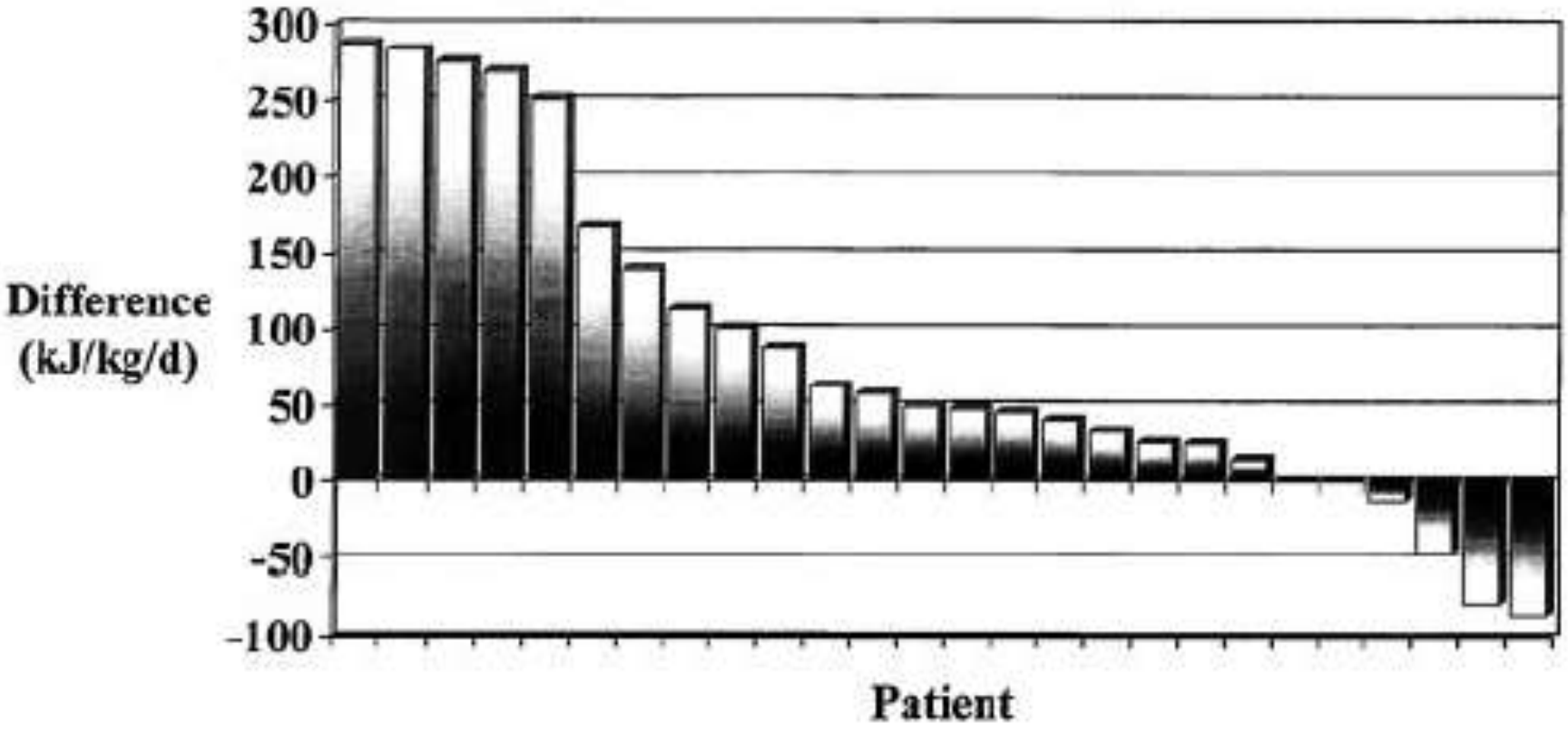
How is nutrient intake affected by treatment?

Table 3 Comparison of energy and nutrient intake between patients and controls

	Patients (n = 53)		Controls (n = 53)		
Nutrients	Mean (SD)	% RNI	Mean (SD)	% RNI	P
Energy [kJ (kcal)]	5732 ± 1958 [1370 (468)]	95	6945 ± 1970 [1660 (471)]*	116	0.005
Carbohydrate (g)	193.5 (64.3)	NA	218.6 (64.7)	NA	0.052
Protein (g)	50.0 (19.7)	185	62.3 (22.3)*	234	0.003
Fat (g)	43.6 (18.9)	NA	58.3 (16.7)†	NA	<0.001
Calcium (mg)	578 (268)	87	684 (368)	108	0.093
Iron (mg)	14.1 (6.4)	177	17.1 (8.8)	217	0.050
Vitamin A (μg RE)	940 (481)	193	1010 (718)	215	0.557
Thiamine (mg)	1.18 (0.60)	166	1.29 (0.79)	193	0.421
Riboflavin (mg)	1.99 (1.40)	278	1.87 (0.95)	278	0.607
Niacin Eq (mg)	15.6 (6.7)	169	15.4 (8.3)	176	0.892
Vitamin C (mg)	64.8 (47.0)	172	49.1 (40.5)	146	0.068

Tan, et al. Journal of Human Nutrition and Dietetics. 2013

Therapy Alters Nutrient Intake



However, response appears to be variable

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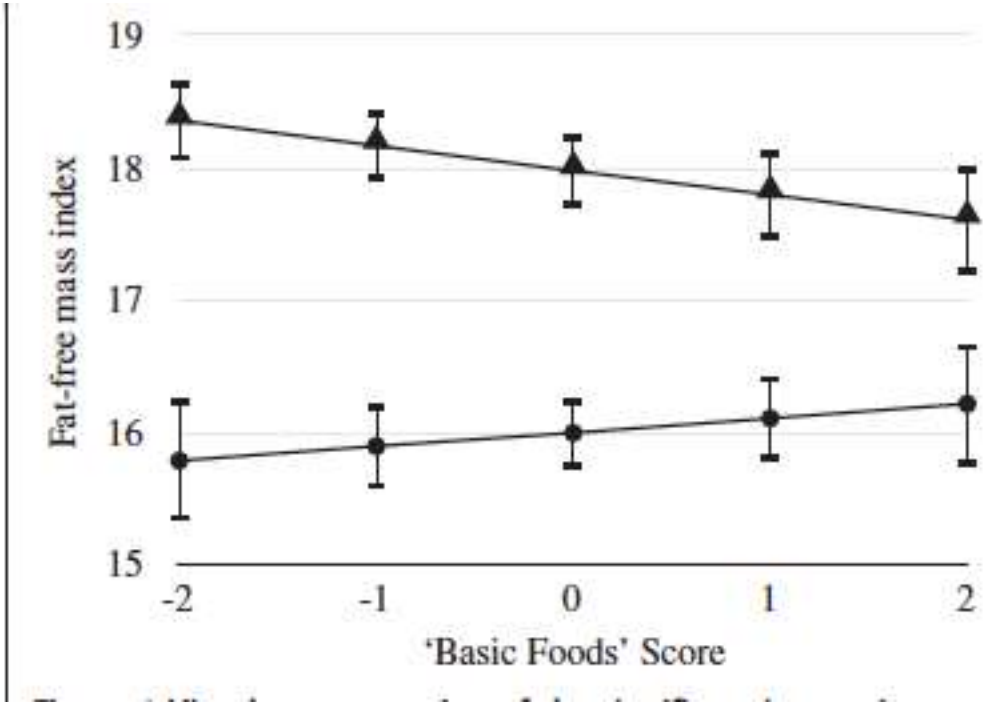
Reilly, et al. J of Endocrinology and Metabolism. 2001

Dietary Intake & Sarcopenic Obesity



"For every SD increase in basic foods score,
A decrease of 3.58% for fat mass index" (Howe, et al 2013)

More to learn…..

- What is the role of dietary intake during treatment and the development of sarcopenic obesity?
- Can diet be modified so as to prevent sarcopenic obesity?
- What role does physical activity have its development?
- Is intervention during treatment feasible?

The Diet and Acute Lymphoblastic Leukemia Treatment (DALLT) Cohort Study

- Prospective Dietary Cohort

Table 2.

Overview of DFCI 05-001 and DALT

Phase	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
Duration	5 Days	4 weeks	3 weeks	3 weeks	27 weeks	~ 70 weeks
Name of Phase	Prophase	Induction	Consolidation	CNS Therapy	Consolidation II	Continuation
Type of Therapy	Steroids	High-Dose Therapy	High-Dose Therapy	Central Nervous System Therapy	High-Dose Therapy	Low-Dose Therapy
Food Frequency Administration	FFQ	FFQ				FFQ

- Harvard Food Service or Youth and Adolescent Food Frequency Questionnaire
- Nutrition support (enteral or parenteral nutrition) was also collected at each timepoint through a
- Therapy-related toxicity data, Survival, Relapse

Table 3. Demographic Characteristics at Study Entry

Demographic Characteristics	Total (N=794)		Complete Survey (N=640)		Did not Complete Survey (N=154)		*p-value*[a]
	Frequency	%	Frequency	%	Frequency	%	
Gender							
Male	444	56%	359	56%	85	55%	0.84
Female	350	44%	281	44%	69	45%	
Age (years)							
1-3	308	39%	248	39%	60	39%	0.46
4-8	262	33%	213	33%	49	32%	
9-13	137	17%	114	18%	23	15%	
14-18	87	11%	65	10%	22	14%	
Ethnicity							
White, Non-Hispanic	507	64%	425	66%	82	53%	< 0.001
Hispanic (White, Hispanic; Other, Hispanic)	142	18%	120	19%	22	14%	
Black (Non-Hispanic, African-American, Black)	38	5%	25	4%	13	8%	
Asian	24	3%	16	3%	8	5%	
Other (Non-Hispanic, Other, Alaskan, American/Indian)	83	10%	54	8%	29	19%	
Language[b]							
English	415	59%	360	56%	55	83%	< 0.001
Spanish	87	12%	85	13%	2	3%	
French	204	29%	195	31%	9	14%	
Risk Group							
Standard Risk	456	57%	372	58%	84	55%	0.42
High Risk	338	43%	268	42%	70	45%	
Geographic Location							
Continental US	429	54%	322	50%	107	69%	< 0.001
Canada	308	39%	264	41%	44	29%	
Puerto Rico	57	7%	54	9%	3	2%	
BMI % at Diagnosis[c]							
<5% (Underweight)	58	7%	44	7%	14	9%	0.38
6-84% (Normal)	508	65%	417	66%	91	61%	
85-94% (Overweight)	120	15%	92	14%	28	19%	
> 95% (Obese)	100	13%	83	13%	17	11%	

[a] *Statistical comparisons were performed using the Pearson's chi-square test. Percentages were rounded to the nearest whole number and may not total to 100%.*

[b] *88 patients were missing primary language information because they did not complete dietary surveys at any timepoint.*

[c] *8 patients were missing BMI % at diagnosis information due to height below 77cm.*

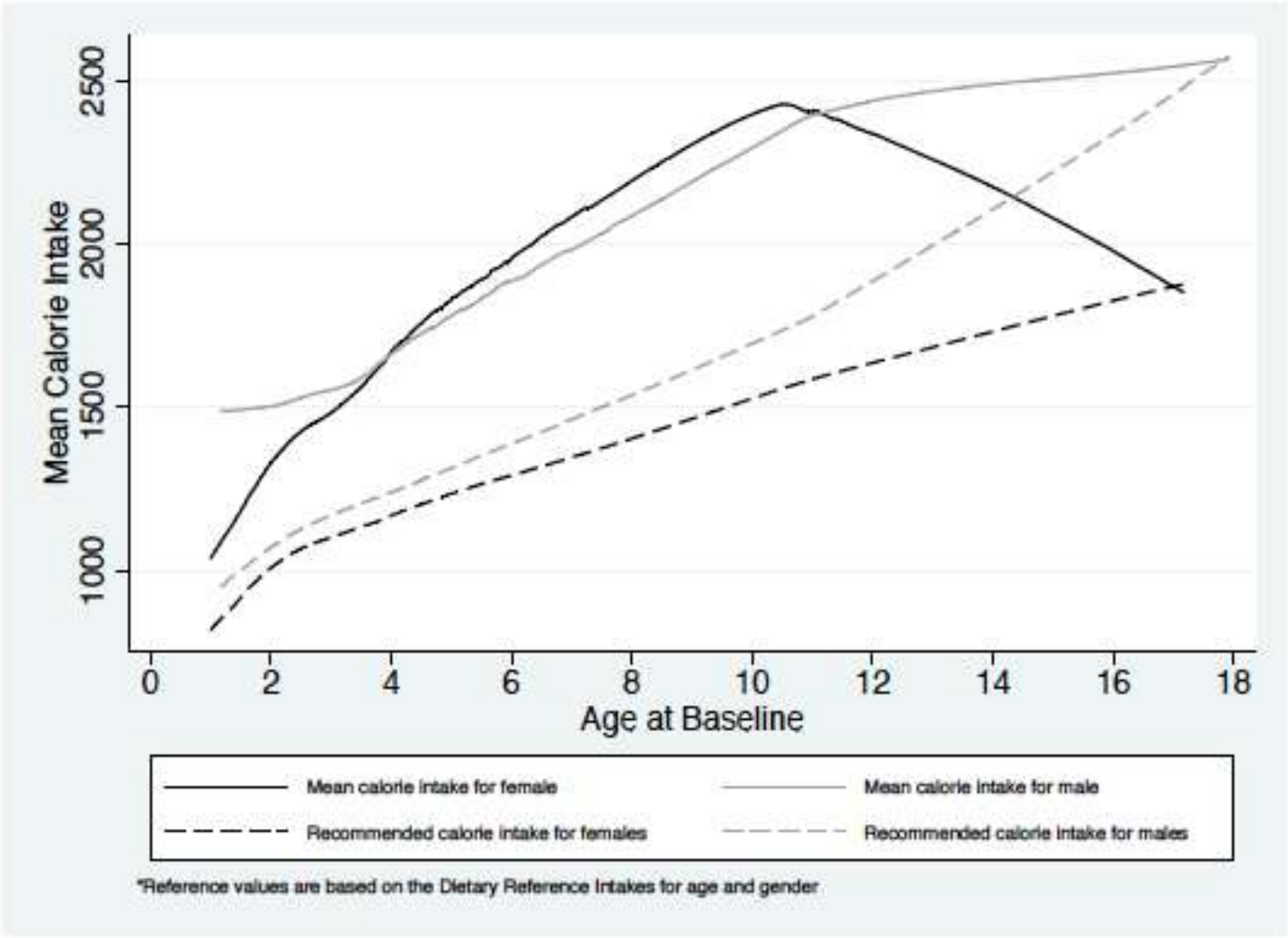
Table 4. Proportion classified as "Under", "Met", "Exceeded" Dietary Reference Intakes (DRI) by Risk Group[a] (N=629)

Nutrient	Male			Female		
	Standard Risk	High Risk	p-value[b]	Standard Risk	High Risk	p-value[b]
Calories						
Under	35 (19%)	34 (21%)	0.30	33 (19%)	14 (14%)	0.98
Met	12 (6%)	14 (9%)		4 (2%)	7 (7%)	
> 10%-24% DRI	26 (14%)	23 (14%)		22 (13%)	14 (14%)	
> 25% DRI	116 (61%)	90 (56%)		117 (67%)	65 (65%)	
% Calories Carbohydrate						
Under	7 (4%)	10 (6%)	0.04	6 (3%)	2 (2%)	0.83
Met	166 (88%)	145 (90%)		161 (92%)	95 (95%)	
Exceed	16 (9%)	6 (4%)		9 (5%)	3 (3%)	
% Calories Fat						
Under	49 (26%)	21 (13%)	< 0.001	40 (23%)	14 (14%)	0.18
Met	124 (66%)	110 (68%)		124 (71%)	80 (80%)	
Exceed	16 (9%)	30 (19%)		12 (7%)	6 (6%)	
% Calories Protein						
Under	1 (1%)	0 (0%)	0.59	0 (0%)	0 (0%)	0.13
Met	186 (98%)	161 (100%)		172 (98%)	100 (100%)	
Exceed	2 (1%)	0 (0%)		4 (2%)	0 (0%)	
Vitamin C (mg)						
Under	8 (4%)	11 (7%)	0.29	13 (7.4%)	12 (12%)	0.20
Met	181 (96%)	150 (93%)		163 (92.6%)	88 (88%)	
Exceed	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Vitamin E (mg)						
Under	148 (78%)	118 (73%)	0.27	136 (77%)	70 (70%)	0.18
Met	41 (22%)	43 (27%)		40 (23%)	30 (30%)	
Exceed	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Zinc (mg)						
Under	5 (3%)	12 (8%)	< 0.001	8 (5%)	10 (10.%)	< 0.001
Met	86 (46%)	102 (63%)		63 (36%)	54 (54%)	
Exceed	98 (52%)	47 (29%)		105 (60%)	36 (36%)	
Calcium (mg)						
Under	62 (33%)	72 (45%)	0.03	55 (31%)	45 (45%)	0.02
Met	126 (67%)	87 (54%)		121 (69%)	55 (55%)	
Exceed	1 (1%)	2 (1%)		0 (0%)	0 (0%)	
Vitamin D (IU)						
Under	179 (95%)	146 (91%)	0.15	167 (95%)	87 (87%)	0.02
Met	10 (5%)	15 (9%)		9 (5%)	13 (13%)	
Exceed	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Folate (mcg)						
Under	14 (7%)	16 (10%)	0.09	11 (6%)	13 (13%)	0.01
Met	83 (44%)	81 (50%)		70 (40%)	47 (47%)	
Exceed	92 (49%)	64 (40%)		95 (54%)	40 (40%)	

[a] Classifications of dietary intake were based on the Dietary Reference Intakes (DRI) by age and gender.
[b] Statistical comparisons were performed using the Mann–Whitney U test. Percentages were rounded to the nearest whole number and may not total to 100%.

Caloric Intake Compared to Normative Values

Figure 1. Mean Calorie Intake by Age and Gender



Final Remarks & Implications

- Nutrition is a **modifiable risk factor** that can improve QOL, reduce toxicity and improve survival in children with cancer.
- Preliminary work suggests **diet quality** may be a factor in nutrition-related toxicities and outcome.
- Sequential observations are **essential** in determining the effectiveness of nutrition interventions.
- Evidence is clear that variations in clinical practice exist and there is a need for more investigators documenting the association of nutrition and outcomes in homogenous cohorts.
- We can't to this alone!
  - International partnering is key in advancing nutritional science, supporting by the success of twinning programs and international collaborative work.

Cancer Control
Nutrition and Integrative Medicine Sub-Committee

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CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Probiotics in Stem Cell Transplant

Brief report

Probiotic effects on experimental graft-versus-host disease: let them eat yogurt

Armin Gerbitz, Michael Schultz, Andrea Wilke, Hans-Jörg Linde, Jürgen Schölmerich, Reinhard Andreesen, and Ernst Holler

Acute graft-versus-host disease (aGVHD) often limits feasibility and outcome of allogeneic bone marrow transplantation. Current pathophysiologic concepts of aGVHD involve conditioning regimens, donor-derived T cells, proinflammatory cytokines, and bacterial lipopolysaccharide (LPS) as a major trigger for aGVHD. LPS derives mostly from gram-negative bacteria and can enter circulation through the impaired mucosal barrier after the conditioning regimen. Probiotic microorganisms have been shown to alter the composition of the intestinal microflora and thereby mediate anti-inflammatory effects. We hypothesized that modifying the enteric flora using the probiotic microorganism *Lactobacillus rhamnosus* GG, would ameliorate aGVHD. Here we show that oral administration of *Lactobacillus rhamnosus* GG before and after transplantation results in improved survival and reduced aGVHD. Furthermore, subculturing of mesenteric lymph node tissue revealed a reduced translocation of enteric bacteria. Our findings suggest that alteration of the intestinal microflora plays an important role in the initiation of experimental aGVHD. (Blood. 2004;103: 4365-4367)

Introduction

Acute graft-versus-host disease (aGVHD) remains one of the major obstacles in allogeneic bone marrow transplantation (BMT). Despite the development of potent immunosuppressive drugs and reduction of conditioning regimens, a high percentage of patients

Study design

Mice, BMT, assessment of GVHD, and treatment protocols

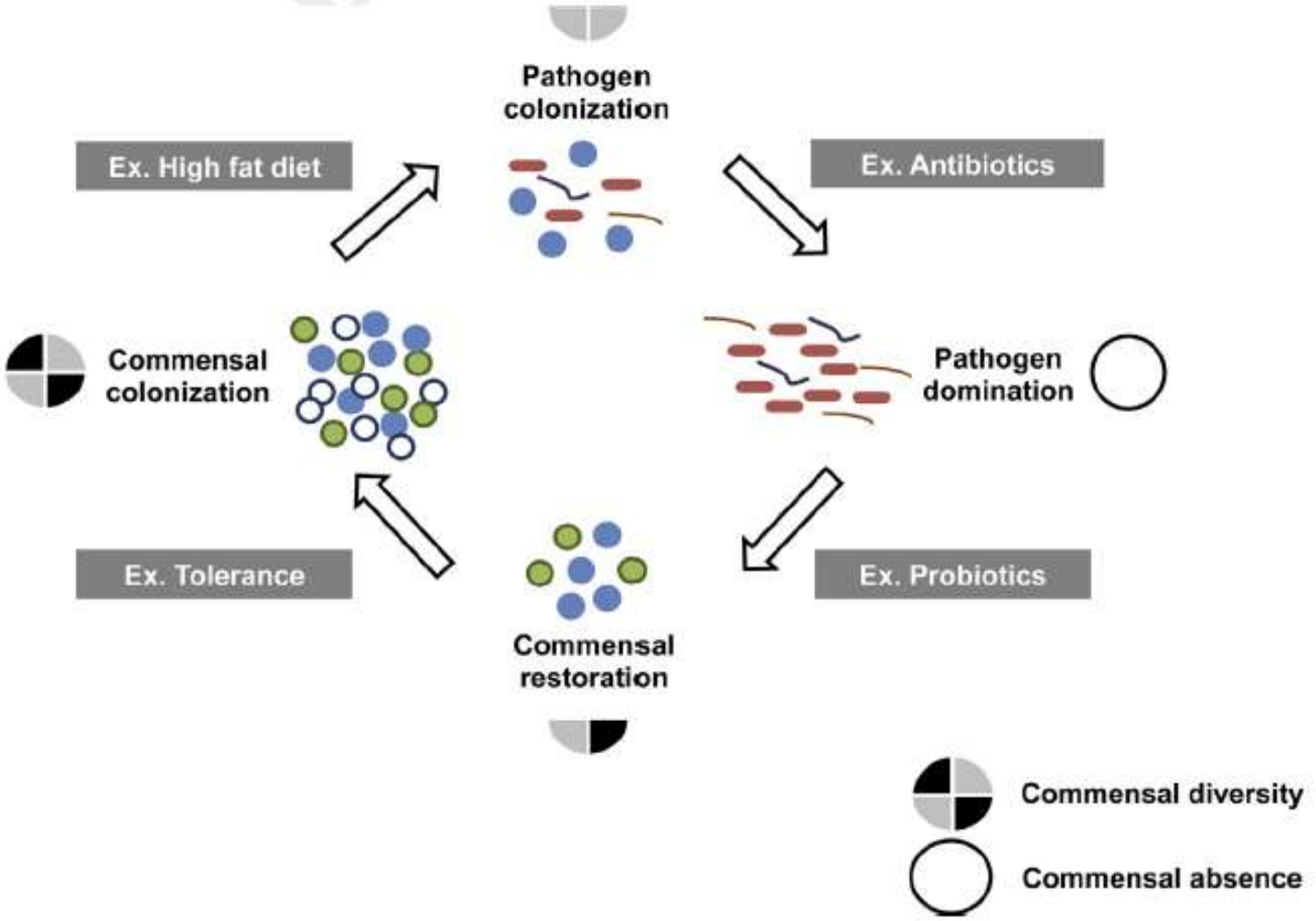
C57BL/6 and B6D2F1 mice (8 to 12 weeks old) were purchased from

Gerbitz, A, et al. Blood 103: 4365-4367. 2004

Acute Graft v Host Disease (aGvHD)

- Clinically significant aGvHD affects approximately 35% of children and adolescents undergoing HCT
- aGvHD can account for up to 20% of the mortality related to transplant
- The GI tract is an important site of aGvHD genesis
- GI aGvHD occurs in appx 25-40% of children and adolescents undergoing allo HCT
- Historically, decontamination therapy was thought to be beneficial for the prevention of aGvHD. No clinical trials were found to support its efficacy.

Intestinal Homeostasis



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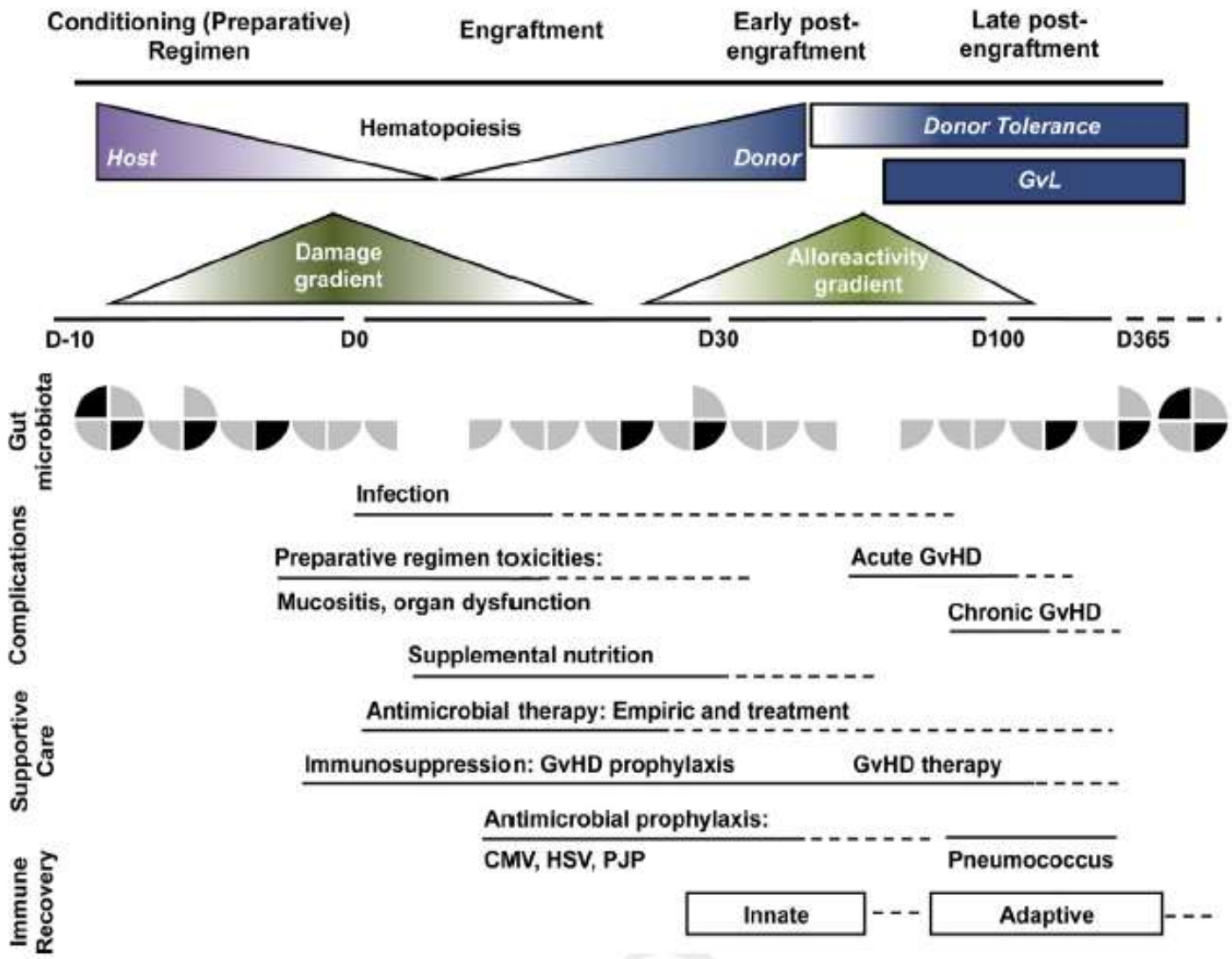
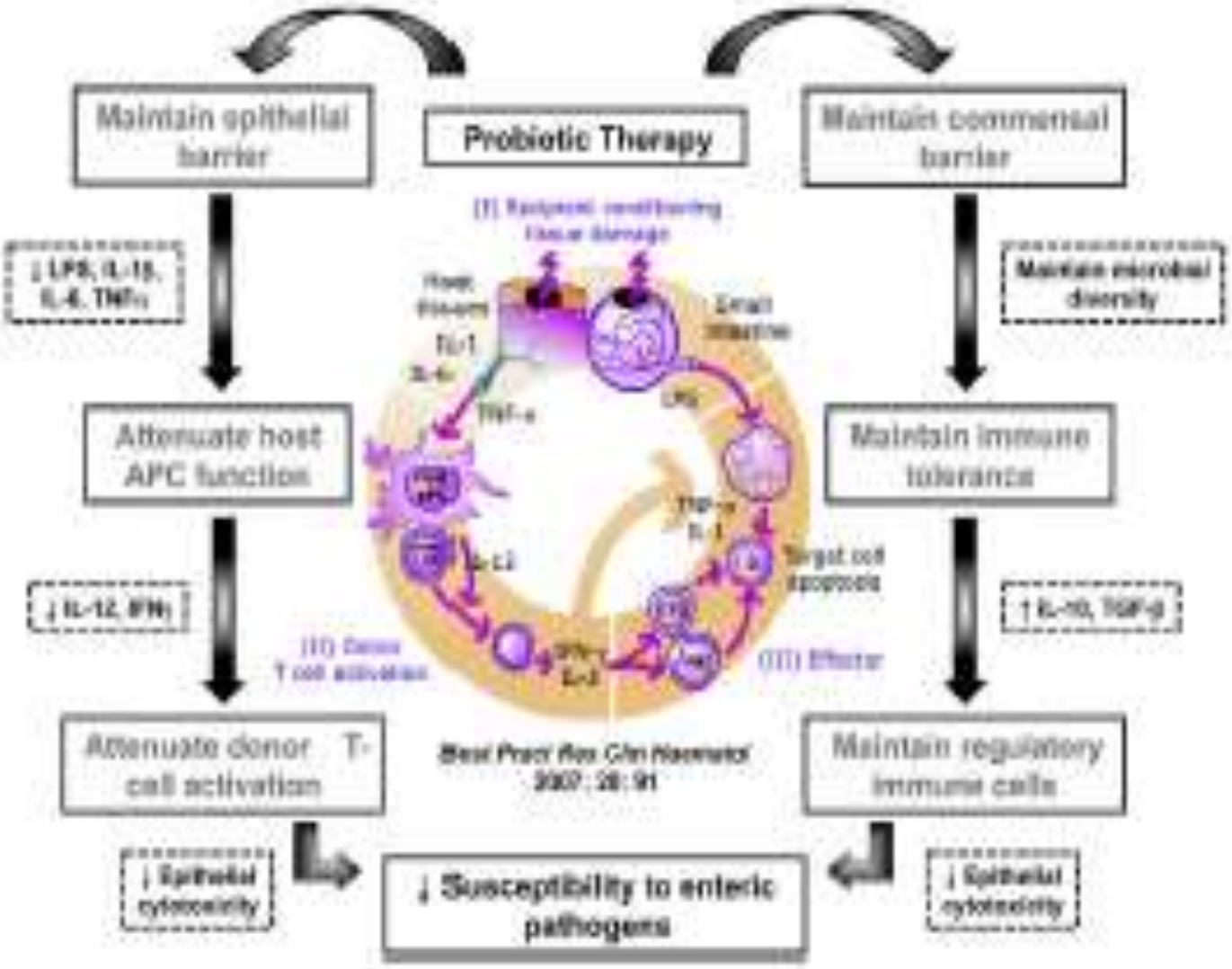


Docampo, et al. Biology Blood Marrow Transplant. 2015
Kariik, et al. Blood Marrow Transplant. 2014

HCT, GvHD and the Intestinal Microbiota

- HCT produces changes in the microbiota.
- A significant relationship exists microbiome diversity and 3-year survival in adults undergoing HCT
  - Low diversity 36%
  - Intermediate diversity 60%
  - High diversity 67%
- Patients who develop GvHD display a characteristic shift in intestinal flora composition.
- Replenishing commensals such as *Lactobacillus* prior to murine HCT substantially decreased aGvHD severity and intestinal insult as well as prevent the sequelae of a number of other HCT-morbidities.
- Microbiota also appears to modulate GvHD-mediated inflammation


Maintain epithelial barrier
Probiotic Therapy
Maintain commensal barrier
↓ LPS, IL-1β, IL-6, TNFα
Maintain microbial diversity
Attenuate host APC function
Maintain immune tolerance
↓ IL-12, IFNγ
↑ IL-10, TGF-β
Attenuate donor T-cell activation
Maintain regulatory immune cells
↓ Epithelial cytotoxicity
↓ Susceptibility to enteric pathogens
↓ Epithelial cytotoxicity

Probiotics

- Probiotics are nutritional supplements that contain a defined amount of viable microorganisms and upon administration confer a benefit to the genesis.
- Clinical trials and systematic analysis have suggested that probiotics are safe and may be beneficial for immune compromised adults, adults with cancer receiving abdominal radiation, and a wide range of pediatric conditions.
- There are many different strains of probiotics; however, few have been explored among immunocompromised individuals.
- *Lactobacillus plantarum* (*LBP*)
  - One of the most thoroughly studied species.
  - Wide safety profile, including immunocompromised adults and children.

Pilot Study

- Pilot trial(IND# 108,977) at Columbia University, All Children's Hospital and Wolfson Children's
- Primary aim was safety of probiotics, *Lactobacillus plantarum* (*LBP*) in a cohort of 30 children and adolescents (ages 2-18 years) undergoing HCT.
- Secondary aims evaluated feasibility and explored clinical outcomes.
- Supplementation with *LBP* began Day -7 of conditioning therapy and continued until Day +14 (22 daily doses).

Ladas et al. Bone Marrow Transplantation 2015

Table 1. Demographic and clinical characteristics

Characteristic	*Evaluable patients (N = 30)*
Institution	
All Children's Hospital, Johns Hopkins Medicine	12 (40%)
New York-Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center	17 (57%)
Nemours Children's Hospital	1 (3%)
Age at enrollment (years)	
Mean (SD)	7.7 (4.7)
Median (range)	6.9 (2.2–17.3)
Age at enrollment (years)	
2–3.99	10 (33%)
⩾4	20 (67%)
Gender	
Female	14 (47%)
Male	16 (53%)
Race	
African American	12 (40%)
Asian	2 (7%)
White	16 (53%)
Diagnosis	
Sickle cell	9 (30%)
Malignancy–leukemia	12 (40%)
Malignancy–lymphoma	1 (3%)
Severe aplastic anemia	4 (13%)
Thalassemia	2 (7%)
Fanconi anemia	1 (3%)
Myeloproliferative disorder	1 (3%)
Donor	
Mismatched unrelated cord	2 (7%)
Mismatched unrelated donor	5(17%)
Matched related donor	12 (40%)
Matched umbilical cord	2 (7%)
Matched unrelated donor	9 (30%)
Stem cell source	
Cord blood	5 (17%)
Marrow	22 (73%)
PBSCs	3 (10%)
Preparatory regimen	
Busulfan–fludarabine-based regimens	13 (43%)
Busulfan–melphalan-based regimens	3 (10%)
Fludarabine–melphalan-based regimens	3 (10%)
TBI–TLI-based regimens	5 (17%)
Cyclophosphomide based regimens	6 (20%)

Ladas et al. Bone Marrow Transplantation 2015

Pilot Study: Safety Results

- No cases of LBP bacteremia
- New onset of *Clostridium difficile* was noted in 20% of the children.

Non-Lactobacillus bacteremia by day 28	
Yes[a]	6 (20%)
Staphylococcus epidermidis	1
Serratia marcescens	1
Enterococcus faecium	1
Klebsiella pneumonia	3
Streptococcus viridans	1
Fusarium species	1
No	24 (80%)

Pilot Study: Compliance

- 30 evaluable patients
  - Mean number of doses taken was 93% (SD 14%)
  - Median was 100% (range 50-100%).
- 31 eligible patients
  - 1/31received less than 50% of the required doses.
- 97% of the eligible patients (30/31), 95% CI (83%-100%), received at least 50% of the prescribed doses.

Pilot Study: Colonization

- Stool samples were collected from 22 of the 30 evaluable patients
- At least one stool specimen was positive for *Lactobacillus* (21/22, 96%).
- Despite this restricted analysis, 77 specimens (75%) were positive for *Lactobacillus*.

Pilot Study: GvHD

- No acute GVHD= 70%
  - 3 patients died prior to Day 100 without developing acute GVHD.
- Grade 1= 0%
- Grade 2= 17% (5 patients)
- Grade 3= 13% (4 patients)
- Grade 4= 0%

Pilot Study: GI GvHD (23%)

- Stage 0: 77% (22 patients)
- Stage 1: 7% (2 patients)
- Stage 2: 3% (1 patient)
- Stage 3: 13% (4 patients)
- Stage 4: 0%

Conclusions

- Administration of *Lactobacillus plantarum* to children undergoing myeloablative Allogenic HCT:
  - Is Safe
  - Is Feasible (excellent compliance)
  - Does not cause an increase in:
    - aGVHD
    - Non-*Lactobacillus* bacteremia
    - *C Difficile*

The Effectiveness of Probiotics in Preventing Acute Graft-versus-Host Disease (GvHD) in Children Undergoing Alternative Hematopoietic Progenitor Cell Transplantation (ACCL1432)

Study Chairs
Michael Nieder, MD; Elena Ladas, PhD, RD; Jeffery Auletta, MD

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Study Hypothesis

Research Hypothesis

- Administration of Lactobacillus plantarum (LBP) probiotic, compared to placebo, will reduce the incidence of gastrointestinal (GI) acute graft-versus-host disease (aGvHD) in children and adolescents undergoing alternative donor hematopoietic cell transplantation (HCT).

Primary Objective:

- To determine whether oral *LBP* reduces the incidence of GI aGVHD in children and adolescents undergoing alternative donor HCT.

Secondary Aims

- To determine whether orally-administered *LBP* decreases the incidence of Grade II–IV aGvHD following alloHCT
- To determine whether *LBP* administration maintains intestinal integrity as measured by mean plasma citrulline levels and reduction in mucosal barrier injury (MBI) bacteremia
- To measure the effects of *LBP* on the intestinal flora phylogenetic composition during and after alloHCT using 16S rRNA gene deep sequencing
- To measure effects of *LBP* on intestinal flora function during and after alloHCT using metagenomic and metabolite profiling
- To measure proposed immunomodulatory effects of *LBP* in mean plasma levels of alloreactive-induced inflammatory cytokines (IL-2, IL-6, IL-12p70, IFNγ, and TNFα) in patients receiving *LBP* compared to placebo.

Inclusion/Exclusion Criteria

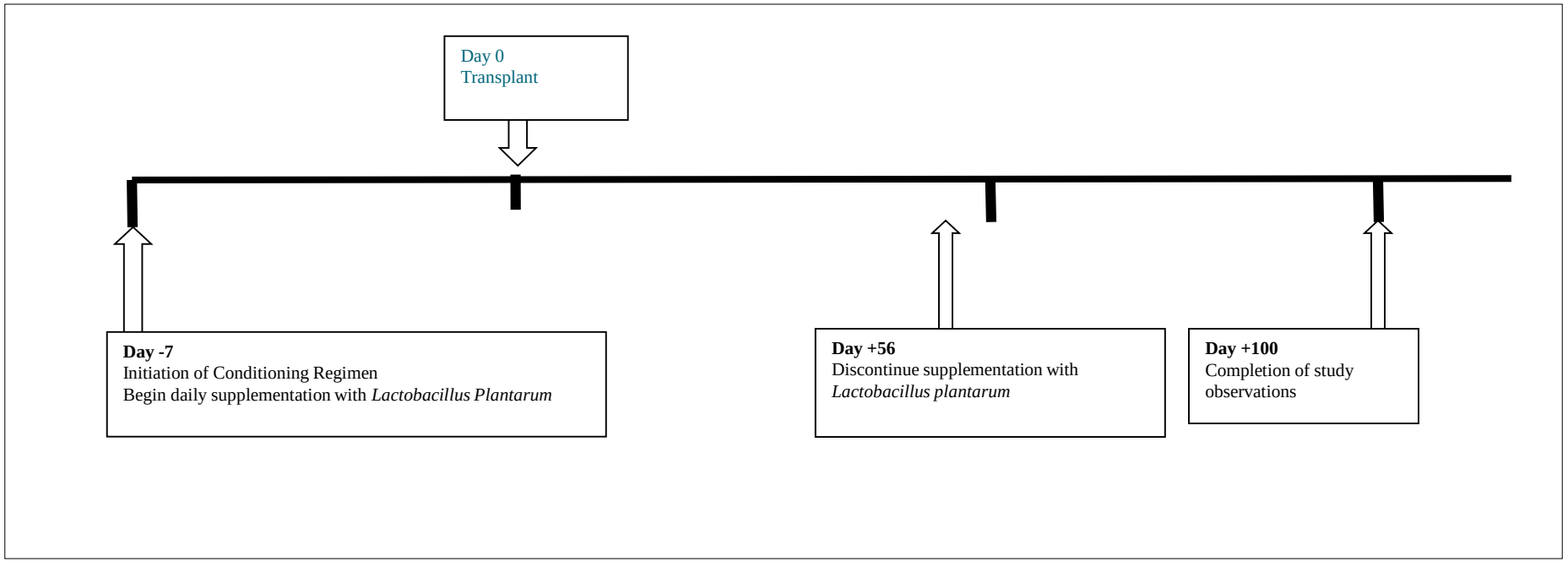
Eligibility criteria

- 2 through 21 years
- First alternative donor (defined as all donors except for matched, related family members) alloHCT
- Hematologic malignancy (leukemia, lymphoma, myelodysplasia)
- Adequate performance status (Lansky/Karnofsky score ≥70)
- Negative *Clostridium difficile* toxin at study entry

Exclusion criteria

- Probiotic use within three months of starting the transplant conditioning regimen (yogurt is allowed)
- History of severe GI tract insult within the past three months such as previous bowel perforations, episode of Grade 4 neutropenic colitis, or typhlitis
- Inflammatory bowel syndrome, short small bowel syndrome, Crohn's disease, ulcerative colitis, or history of bowel resection
- Use of anti-microbial gut decontamination or keratinocyte growth factor (KGF)
- Active infection at the initiation of conditioning regimen

Study Schematic



Incidence: GI aGvHD is ~ 30 % in alternative donor transplants.
Success: Defined as a 25% relative reduction in GI aGVHD.
Estimated sample: N= 384

International Society Pediatric Oncology, Pediatric Oncology Developing Countries, Nutrition Committee

Chairs:

Brijesh Arora, MD (India)

Elena J Ladas, PhD, RD (United States)

SIOP-PODC Nutrition

- **Lectures via Cure4Kids**
  - Continue to hold monthly nutrition lectures via Cure4Kids (3rd Tuesday every month, 10am EST)
  - Collaboration with other SIOP Committees (neuroblastoma group, infection control)
  - Membership continues to grow. Current members: 92 representing 24 countries and all continents.
- **Regional Workshops**
  - 1st workshop held in November 2014 held in Mumbia, India (trained over 200 clinicians)
  - 2nd workshop held at SIOP Asia Workshop (Amman, Jordon on April 23, 2015)
    - 152 clinicians trained in nutrition and pediatric oncology
    - Lectures were also provided at two of the major hospitals in Amman (Queen Raina Hospital and King Hussein Cancer Center)

SIOP-PODC Nutrition

- **Regional Workshops**
  - Sao Paolo, Brazil (November 12/13, 2015)
    - Over 100 attendees
    - Summary statistics of the conference were overwhelmingly positive.
    - 98% reported that conference met expectations
    - 99% reported that the conference improved their knowledge of nutrition
    - 99% reported that the conference will improve their clinical practice
  - Mumbai, India (February 6/7, 2016)
    - 100% of participants reported that the conference met expectations
    - 100% of participants reported that the conference improved their knowledge of nutrition and this can be applied to their clinical practice.
- **Upcoming Workshops**
  - SIOP Asia (Moscow, Russia): May 25, 2016.
  - Rio de Janeiro (November 2016).
  - Planning is underway for 2017
    - SIOP Asia- Bangkok, Thailand
- **Fellowship Training in Mumbai**
  - Started fellowship program
  - First fellowship trained 22 nutritionists from 8 centers in India, included 70 lectures.
  - Second fellowship trained 43 nutritionists from 32 centers in India.

A Framework for Adapted Nutritional Therapy for Children With Cancer in Low- and Middle-Income Countries: A Report From the SIOP PODC Nutrition Working Group

Elena J. Ladas, PhD, RD,[1,2*] Brijesh Arora, MD, DM,[3] Scott C. Howard, MD,[4] Paul C. Rogers, MD,[5] Terezie T. Mosby, EdD, RD,[6] and Ronald D. Barr, MB ChB, MD[7]

The utilization of adapted regimens for the treatment of pediatric malignancies has greatly improved clinical outcomes for children receiving treatment in low- and middle-income countries (LMIC). Nutritional depletion has been associated with poorer outcomes, increased abandonment of therapy, and treatment-related toxicities. Surveys have found that nutritional intervention is not incorporated routinely into supportive care regimens. Establishing nutritional programs based upon institutional resources may facilitate the incorporation of nutritional therapy into clinical care in a way that is feasible in all settings. We present a framework for establishing and monitoring of nutritional care based on the infrastructure of institutions in LMIC. Pediatr Blood Cancer 0000;00:000–000.

Key words: adapted guidelines; international outreach; low- and middle-income countries; nutrition; nutritional status

INTRODUCTION

The treatment of cancer in childhood is often described as a success story. In a little over four decades, cure rates have risen to approximately 80% for children and adolescents who live in high-income countries (HIC).[1] Unfortunately, this figure is not reflective of regions where most children with cancer reside. At least 80% of children diagnosed with a malignancy live in low- or middle-income countries (LMIC) where limited access to treatment, essential medications, and trained clinicians are barriers to receiving optimal therapy.[2] Despite these challenges, a considerable number of children who live in LMIC are surviving cancer. For example, in some parts of Central America, survival abandonment of therapy.[11] Subsequent studies have reported that remediation of poor nutritional status mitigates the negative association with survival.[12,13]

Oncologists practicing in LMIC often have a higher volume of patients compared to their colleagues in HIC; therefore, nutritional therapy is often delayed or ignored due to allocation of time directed toward life-saving cancer treatment.

Additional supporting information can be found in the supporting information tab for this article.

Abbreviations: BMI, body mass index; EN, enteral nutrition; GT,

SIOP-PODC Nutrition Research

- **Research**
  - RUTF trial (PI: B. Arora)
  - SCAN feasibility (PI: A. Murphy)
  - Algorithm validation (PIs: C Fleming, K Viani)
- **Grant Awards**
  - Nutritional status in children with cancer in Guatemala (F Antillon, R Barr, E Ladas)
  - Mullen Foundation- Build Capacity in LMIC (PI: E Ladas Co-PI: B Arora, R Barr)

Development of a Nutrition Research & Training Program in India

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THANK YOU!

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