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## No Obesity Paradox in Pediatric Patients with Dilated Cardiomyopathy

Chesney D. Castleberry, MD<sup>1</sup>, John L. Jefferies, MD, MPH<sup>2</sup>, Ling Shi, PhD<sup>3</sup>, James D. Wilkinson, MD, MPH<sup>4</sup>, Jeffrey A. Towbin, MD<sup>5</sup>, Ryan W Harrison, BS<sup>3</sup>, Joseph W. Rossano, MD, MS<sup>6</sup>, Elfriede Pahl, MD<sup>7</sup>, Teresa M. Lee, MD<sup>8</sup>, Linda J. Addonizio, MD<sup>8</sup>, Melanie D. Everitt, MD<sup>9</sup>, Justin Godown, MD<sup>10</sup>, Joseph Mahgerefteh, MD<sup>11</sup>, Paolo Rusconi, MD<sup>12</sup>, Charles E. Canter, MD<sup>1</sup>, Steven D. Colan, MD<sup>13</sup>, Paul F. Kantor, MBBCh<sup>14</sup>, Hiedy Razoky, BS, MBA<sup>4</sup>, Steven E. Lipshultz, MD<sup>4</sup>, and Tracie L. Miller, MD<sup>12</sup>

<sup>1</sup>Washington University School of Medicine, St. Louis, MO

<sup>2</sup>The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

<sup>3</sup>New England Research Institutes, Watertown, MA

<sup>4</sup>Wayne State University School of Medicine and Children's Hospital of Michigan, Detroit, MI

<sup>5</sup>The Heart Institute, Le Bonheur Children's Hospital, Memphis, TN

<sup>6</sup>The Children's Hospital of Philadelphia, Philadelphia, PA

<sup>7</sup>Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

<sup>8</sup>Columbia University Medical Center, New York, NY

<sup>9</sup>Children's Hospital Colorado, University of Colorado, Aurora, CO

<sup>10</sup>Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN

<sup>11</sup>Children's Hospital at Montefiore, Bronx, NY

<sup>12</sup>University of Miami, Miller School of Medicine, Miami, FL

<sup>13</sup>Boston Children's Hospital, Boston, MA

<sup>14</sup>Stollery Children's Hospital, University of Alberta, Edmonton, AB, Canada

### Abstract

**Background**—In adults with dilated cardiomyopathy (DCM), malnutrition is associated with mortality while obesity with survival. We aimed to examine the role of nutrition in pediatric DCM.

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**Address for correspondence:** Chesney D. Castleberry, MD, Washington University in St. Louis, One Children's Place, Campus Box 8116- NWT, St. Louis, MO 63110, Phone: (314) 454-6095, Fax: (314) 454-2561, castleberry\_c@kids.wustl.edu.

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### DISCLOSURES

None

**Methods**—NHLBI-funded Pediatric Cardiomyopathy Registry was used to identify DCM patients and categorized by anthropometric measurements: malnourished (MN, body mass index (BMI) <5% for <2 years or weight-for-length <5% for <2 years), obesity (BMI > 95% for age <2 years or weight-for-length >95% for <2 years), or normal bodyweight (NB). Of 904 DCM patients, 23.7% (214) were MN, 13.3% (120) were obese, and 63.1% (570) were NB.

**Results**—Obese patients were older (9.0 vs. 5.7 years for NB,  $P < 0.001$ ) and more likely to have a family history of DCM (36.1% vs. 23.5% for NB,  $P = 0.023$ ). MN patients were younger (2.7 years vs. 5.7 years for NB,  $P < 0.001$ ) and more likely to have heart failure (79.9% vs. 69.7% for NB,  $P = 0.012$ ), cardiac dimension z-scores > 2, and higher ventricular mass compared to NB. In multivariable analysis, MN was associated with increased risk of death (HR: 2.06, 95% CI: 1.66-3.65,  $P < 0.001$ ); whereas, obesity was not (HR: 1.49, 95% CI: 0.72, 3.08). Competing outcomes analysis demonstrated increased risk of mortality for MN compared to NB ( $P = 0.03$ ), but no difference in transplant rate ( $P = 0.159$ ).

**Conclusions**—Malnutrition is associated with increased mortality and other unfavorable echocardiographic and clinical outcomes compared to those with NB. The same effect of obesity on survival was not observed. Further studies are needed investigating the long-term impact of abnormal anthropometric measurements on outcomes in pediatric DCM.

**Clinical Trial Registration**—NCT00005391; <https://clinicaltrials.gov/ct2/show/NCT00005391?term=NCT00005391&rank=1>

### Keywords

dilated cardiomyopathy; pediatrics; heart failure

### Subject Terms

diet and nutrition; obesity; pediatrics; cardiomyopathy; heart failure

## INTRODUCTION

Children with heart failure are at increased risk for developing malnutrition given higher than normal energy requirements.<sup>1</sup> Poor growth is frequent even in patients receiving supplemental enteral feedings.<sup>2</sup> In children undergoing heart transplant, malnutrition has been implicated as a risk factor for mortality before and after transplant.<sup>3,4</sup>

Obesity is another important consideration in the pediatric population. Adults with obesity are at increased risk for developing heart failure.<sup>5,6</sup> Although obesity is a risk factor for mortality after heart transplant in adults, an “obesity paradox” exists where obese adults with systolic dysfunction or clinical symptoms of heart failure survive longer than adults who are malnourished or are of normal weight.<sup>7-10</sup> The mechanism of this difference in outcomes is not well understood and has not been investigated in children.<sup>11</sup> Because the rate of childhood obesity and metabolic syndrome is now sufficiently high, encountering children with cardiomyopathy and obesity is no longer uncommon.<sup>12</sup>

The primary aim of this study was to describe the impact of malnourishment and obesity on clinical outcomes (death or heart transplantation) in children with dilated cardiomyopathy (DCM). We hypothesized that there would be an increased frequency of death or transplantation in malnourished patients while obesity would not adversely impact death or transplantation compared to patients with normal anthropometric measurements.

## METHODS

The National Heart, Lung, and Blood Institute-funded Pediatric Cardiomyopathy Registry (PCMR) was used to identify patients with DCM. This registry consists of demographic, echocardiographic, and clinical data on over 3,000 children (age <18 years at diagnosis) with cardiomyopathy diagnosed at any of 98 pediatric cardiac centers in the United States and Canada since the registry was established in 1990. Data, including anthropometric and echocardiographic data, are collected within 30 days of diagnosis and enrollment in the study as well as annually until a patient reaches the age of 18 years. Each participating center obtains Institutional Review Board or Ethics Committee approval for the study. Detailed information regarding registry design and conduct are detailed elsewhere.<sup>13,14</sup> Data used for this study were frozen on January 14<sup>th</sup>, 2013.

The PCMR defines DCM based on echocardiographic measurements of ventricular size and function, pathological findings on biopsy or autopsy, or clinical diagnosis.<sup>15</sup> Patients with a neuromuscular disorder, malformation syndrome, or inborn error of metabolism were excluded from the current analysis because the underlying disease in these patients was believed to influence outcomes independently of DCM. Patients were also excluded if weight or height measurements were not available in the registry.

Participants were categorized into one of three mutually exclusive nutrition groups based on anthropometric measurement at time of diagnosis. The categories were: Malnourished (MN), Normal Bodyweight (NB), and Obese. Participants two years of age and older were considered MN if their BMI was lower than the 5<sup>th</sup> percentile for age and gender, and, participants less than two years were considered MN if their weight-for-length was less than the 5<sup>th</sup> percentile. Participants two years of age or older were considered obese if their BMI for age and gender was above the 95<sup>th</sup> percentile, and participants younger than two years were obese if their weight-for-length was greater than the 95<sup>th</sup> percentile.

Echocardiographic variables, including LV end-diastolic dimension (EDD), posterior wall thickness, septal thickness, and mass, were expressed as z-scores conditional on body surface area and calculated using best possible fit with BSA as the determinant and were determined using the lambda mu sigma (LMS) method as described by Foster et al (Sluysmans and Foster). Left ventricular fractional shortening (LVFS) and posterior wall thickness to end diastolic diameter ratio were expressed as the z-score conditional on age.<sup>16</sup>

The New England Research Institutes (Watertown, MA) was the PCMR Data Coordinating Center and performed all data analyses. To describe the patients' characteristics and baseline echocardiographic parameters, means and standard deviations were used for normally distributed variables and frequencies and percentages were used for categorical variables.

Analysis of variance (ANOVA) and Chi-square test were used to assess overall differences across the three nutritional groups. Kaplan-Meier plots of time from diagnosis to death and/or transplantation were generated, and log rank P-values were calculated. Patients were censored at seven years given duration of study follow-up.

### Statistical Methods

Analysis of variance (ANOVA) and Chi-square test were used for overall comparison across the nutritional groups. Pair-wise comparisons were conducted when the overall p value is < 0.05. Post-hoc Bonferroni-corrected P values < 0.017 (0.05/3 comparison groups) were considered statistically significant. Cox proportional hazard regression models were used to determine impact of nutritional status on survival and freedom from transplant as the outcome of interest while adjusting for potential confounders. First, univariate Cox regression models were fit for a selection of predictors which were chosen based on prior knowledge that were potentially associated with survival outcomes, then multivariable Cox regression models were fit step by step by adding covariates that were significant in the univariate analyses at the <0.10 level, including age, congestive heart failure, anti-congestive therapy, FS z-score, HAZ, and ratio of LV EDPT/EDD z-score. Finally, backwards model selection was used to determine the final model. To test the proportionality assumption, the Kaplan-Meier plots were used to check the proportional hazards for categorical covariates, while scatterplot smooths were used to examine the relationship between scaled Schoenfeld residuals and follow-up time for continuous covariates. We also assessed proportional hazards assumption by testing the interaction between the covariate and the follow-up time. Estimates of cumulative incidence for each of the three competing outcomes (death, transplantation, or survival and freedom from transplant) were calculated in the competing risk analysis. Statistical significance was established at a P-value <0.05. Analysis was performed using SAS version 9.3 (Cary, NC) and R version 3.1.1.

## RESULTS

There were 1,755 DCM patients who did not have neuromuscular disorder, malformation syndrome or an inborn error of metabolism. Of the 1,755 participants who met inclusion criteria, 851 were excluded due to missing height and weight measurements. Demographics of excluded patients are included in Appendix A and revealed younger age and a different race distribution among excluded patients (Appendix A). The study population therefore included 904 participants with documented height and weight information. Of these participants, 23.7% (214) were MN, 63.1% (570) were NB, and 13.3% (120) were obese. The median follow up time was 1.4 years (mean  $\pm$  SD: 2.8  $\pm$  3.4 years) for all participants, 1.3 (3.0 $\pm$ 3.8), 1.6 (2.9 $\pm$ 3.4), and 0.9 (1.9 $\pm$ 2.7) years for MN, NB, and obese participants, respectively. MN patients were more likely to be younger, have a lower weight-for-age z-score, have heart failure at time of diagnosis and receive anti-heart failure therapy compared to patients with NB (P<0.05 for all). Compared to NB, obese patients were more likely to be older, have lower height-for-age z-score, higher weight-for-age z-score, and have a family history of cardiomyopathy (P<0.05 for all). These patterns were similar for MN compared to obese with MN being younger, more frequently female, greater height-for-age z-score, lower weight for age z-score, lower BMI, more heart failure at diagnosis and on anti-heart failure

therapy. Otherwise, there were no significant differences between the groups by race, etiology, family history of sudden death, or anti-heart failure therapy (Table 1).

Echocardiographic features differed amongst the anthropometric classifications (Table 2). MN patients had larger left ventricular (LV) end-diastolic and systolic dimension z-scores than those with NB ( $P<0.001$ ). LV fractional shortening z-scores were lower in MN patients ( $P<0.001$ ); however, there was no difference in LV posterior wall thickness to end diastolic diameter ratio and ejection fraction z-scores. There was also no difference in percentage of patients with mitral regurgitation or left atrial dilatation between the study groups (Table 2).

Logarithmic test from Kaplan-Meier analysis demonstrated that there was decreased survival in both MN and obese patients compared to NB (84.7% transplant-free survival in MN patients and 86.2% in obese patients), compared to 91.8% in NB patients at two years post-diagnosis ( $P=0.01$  and  $P=0.02$ , respectively) (Table 3, Figure 1A) with a corresponding increase in event rate (56.3 and 64.5 events/1000 person-years respectively compared to 32.2 in NB participants). There was an increased risk of death or transplant as a composite endpoint in obese vs. NB patients (55.9% 2-year transplant free survival and 248 events/1000 person-years) in obese patients compared to 67.4% and 132.8 events/1000 person-years in NB;  $p=0.016$  (Table 3, Figure 1B), though no difference was seen in MN vs. NB ( $p=0.191$ ). Conversely, in competing risk analysis, there was increased mortality in MN patients compared to NB ( $p=0.030$ ), but not between obese and NB ( $p=0.223$ ). The cumulative incidence rate of death in this analysis was 19.1% in MN patients, significantly higher than the 13.0% in NB patients; however, there was no difference between the groups in rate of transplantation between any of the nutritional groups ( $p=0.159$ ) (Figure 2).

In multivariable model derived from univariate analysis, there was an increased risk for death in MN patients compared to NB patients (2.06 hazard ratio (HR), 95% CI: 1.17, 3.65;  $p=0.042$ ). When risk for death or transplant was analyzed, MN was not associated with greater risk for death or transplant compared to NB patients. Likewise, there was no increased risk of listing for transplant in the MN patients. There was also no increased risk of death, death or transplant, or transplant alone in obese patients compared to those who were NB ( $p>0.05$  for all) (Table 3).

Sub-analysis was performed to determine the impact of MN and obesity on survival, stratified by age (< 1 year, 1-10 years, and >10 years). There was no difference in transplant-free survival between patients of different nutritional status based on age ( $p>0.05$  for all) (Figure 3).

## DISCUSSION

In this study from one of the largest registries in pediatric cardiomyopathy with data collection from over 98 pediatric cardiac centers in the United States and Canada that includes patients from the time of diagnosis of DCM, we found that MN was a significant risk factor for death after diagnosis of DCM. Additionally, there was decreased overall survival in obese pediatric patients, though obesity was not associated with increased mortality in multivariable analysis.

Our findings of higher mortality in pediatric DCM with MN have been noted in other pediatric heart failure cohorts. Malnutrition has been associated with increased mortality in pediatric patients listed for transplant.<sup>17–20</sup> The higher mortality seen in this population is believed to be secondary to an increase in neurohormonal and inflammatory activation that leads to further increases in metabolic demands while tolerance of feeds diminishes due to gut perfusion.<sup>2</sup> Additionally, heart failure leads to maladaptive gastrointestinal responses which produce decreased appetite, poor absorption of nutrients, and increased protein catabolism.<sup>20</sup> These patients have higher rates of emergency room visits and hospitalizations, hospital morbidities, and all-cause mortality.<sup>21–23</sup>

Though malnutrition leads to adverse outcomes in pediatric patients both before and after transplant, it has not been an established risk factor in pediatric patients prior to listing for transplant.<sup>17,18</sup> We saw that like patients with end stage heart disease, malnutrition remained a significant risk factor for mortality in all comers with DCM. This suggests that early recognition of malnutrition in this patient population could potentiate outcomes and should be a focus of future study.

Obesity is associated with heart failure in both the adult and pediatric general populations.<sup>5, 6</sup> This is believed to be secondary to an obesity-related increased heart rate and stroke volume that leads to left ventricular concentric remodeling (normal left ventricular mass with elevated mass-to-volume ratio), and subsequently increased LV mass and diastolic dysfunction.<sup>24–26</sup> This can progress to LV systolic dysfunction and dilation.<sup>26</sup> Length of time with obesity is associated with lower LV systolic function and greater diastolic dysfunction.<sup>27,28</sup> These effects are independent of hypertension or other cardiovascular risk factors.<sup>29</sup>

The impact of obesity on outcomes in patients with heart failure is not well understood. Several large studies have demonstrated that obese patients do better than those with normal weight including decreased mortality and hospitalizations, leading to the theory of the existence of an “obesity paradox.”<sup>30,31</sup> This has been confirmed in the meta-analysis by Sharma et al where MN was associated with increased mortality; however, obesity was associated with lower risk of hospitalization and cardiovascular mortality.<sup>30</sup> Mechanisms postulated that are believed to be associated with this difference in outcome include greater metabolic reserve, protective cytokines, attenuated response to renin-angiotensin-aldosterone system, or different cause of heart failure among others.<sup>30</sup> Recent data, however have challenged the link between obesity and decreased mortality, suggesting that it is explained by a confounding bias within the population.<sup>11</sup> Additionally, these patients may be more closely monitored for cardiac complications and have incidental ventricular dilation from obesity related adaptive changes.<sup>6</sup> Thus clinical symptoms related to obesity are often unrelated to cardiac causes.<sup>32–34</sup> Gustafsson found that heart failure patients with a preserved LV ejection fraction demonstrated better survival and that outcome was worse in patients with obesity and depressed LV systolic function compared to patients with normal anthropometric measurements.<sup>35</sup> Although we found that there was decreased event-free survival in obese patients, obesity itself was not a risk factor for death in this pediatric cardiomyopathy population as a whole, including symptomatic and asymptomatic individuals.

Malnutrition and obesity are both significant considerations in transplant suitability given the increased risk of post-transplant morbidity and mortality.<sup>36</sup> Because of the impact of obesity in particular on morbidity post-transplant, current International Society for Heart and Lung Transplantation recommendations for adult candidates are to delay listing for transplantation until patients reach a BMI <35 kg/m<sup>37</sup> Neither obesity nor malnutrition was found to impact frequency of transplantation in our pediatric cohort.

The impact of malnutrition or obesity may not be the same across all age ranges. For instance, infants with malnutrition may have worse outcomes given their limited reserve.<sup>20</sup> Likewise, obesity may have a greater impact in older patients, especially adolescents, given that the chronicity of obesity has been shown to impact outcomes.<sup>38</sup> Though there were no differences seen in the age subgroups, there was a trend towards worse survival over time for both malnutrition and obesity across all age groups.

### Limitations

Though the patient cohort studied was large, one significant limitation was the amount of missing height and weight data in the population. These patients were also sicker (Appendix B), possibly reflecting the difficulty obtaining accurate height and weight measurements in patients who present in extremis. Also, body composition, including lean or fat mass, as estimates of nutritional status was not collected in the registry and body surface normalization through the use of standardized z-scores for echocardiographic measurements may be misleading at the extremes of the weight spectrums. Information regarding body composition, especially for patients meeting criteria for malnutrition, is largely unknown and not part of the registry. Weight information was collected prospectively at the time of enrollment; however, detailed information regarding presence or absence of edema is also unknown. Information on clinical symptoms, including New York Heart Association and Ross classification of heart failure, was available for too few patients to allow inclusion of symptomatic status in the analysis.

### CONCLUSIONS

Malnutrition is associated with an increased risk of death after the diagnosis of DCM. Additionally, obesity was not protective in this population as it is in adults; and there was, in fact, decreased overall survival in the obese population compared to the NB. However, obesity itself was not an explanatory factor. Neither malnutrition nor obesity was associated with a significant difference in rate of transplantation compared to the normal body weight. Prospective studies of nutritional interventions are needed to understand influence of nutritional status on clinical outcomes in children with dilated cardiomyopathy.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## ABBREVIATIONS

<b>DCM</b>	dilated cardiomyopathy
<b>MN</b>	malnourished
<b>BMI</b>	body mass index
<b>NB</b>	normal bodyweight
<b>PCMR</b>	pediatric cardiomyopathy registry
<b>EDD</b>	end-diastolic dimension
<b>LVFS</b>	left ventricular fractional shortening
<b>LV</b>	left ventricular
<b>HR</b>	hazard ratio
<b>HR</b>	heart rate
<b>NHLBI</b>	national heart lung and blood institute

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### CLINICAL PERSPECTIVES

Our study has significant implications for both the pediatric and population. Ongoing emphasis on improving nutrition in patients with dilated cardiomyopathy is important as it has significant prognostic implications, thus providing an avenue to improve clinical outcomes. Likewise, obesity should be taken seriously in this patient population, as there was no association with decreased morbidity. Lifestyle modification in these young patients is most likely an avenue for improving outcomes, as this factor is also potentially modifiable.

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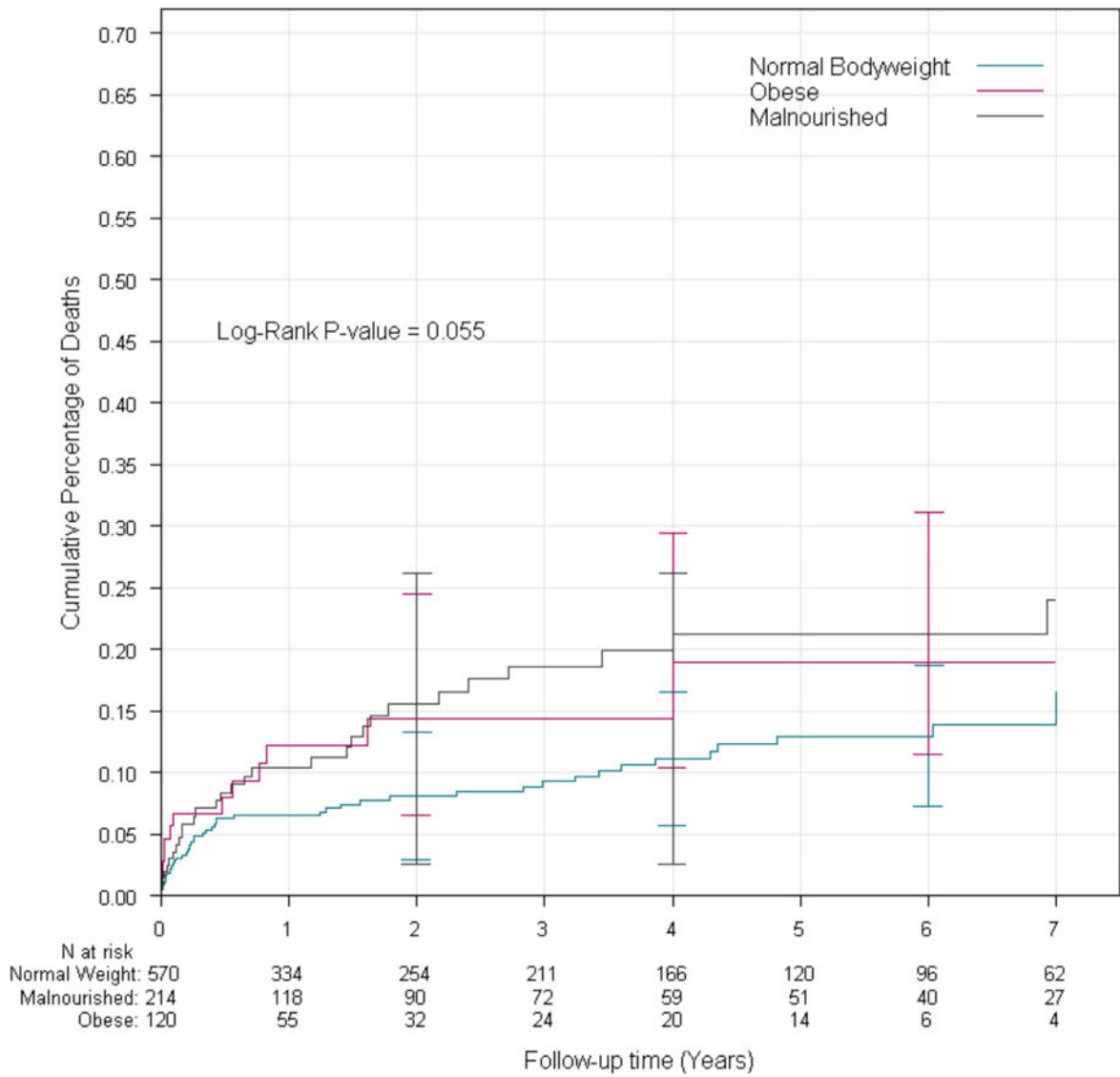
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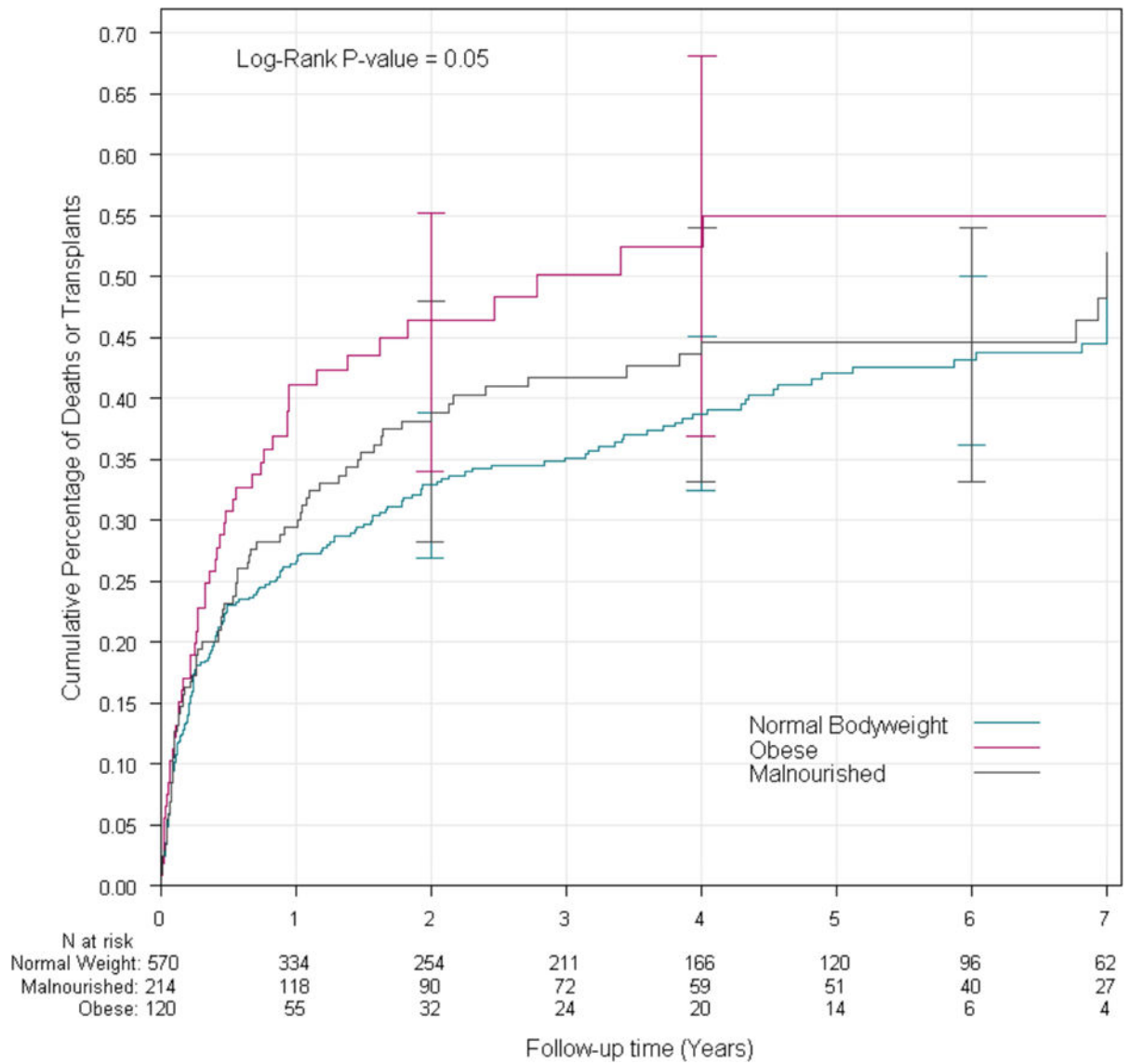
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### TRANSLATIONAL OUTLOOK

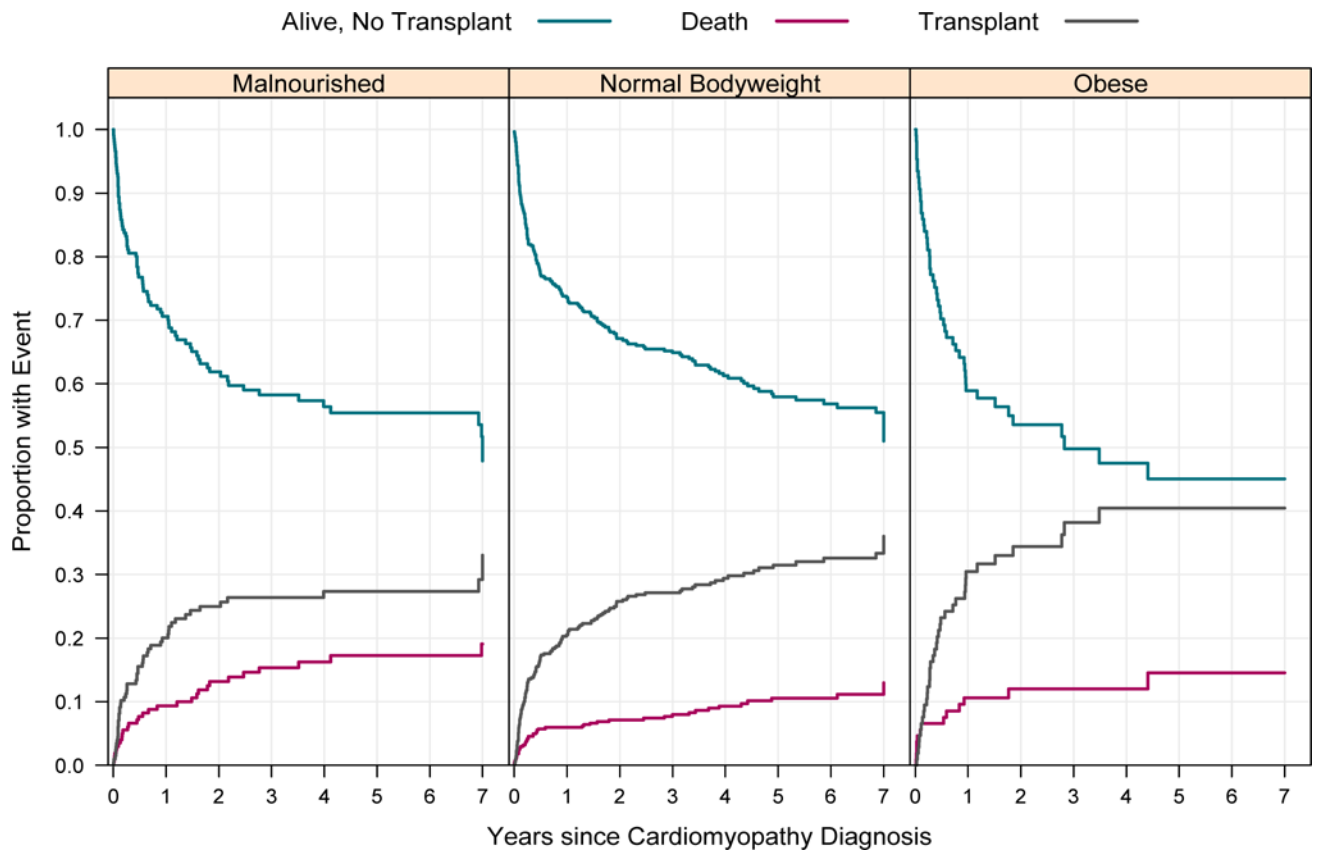
Future studies are needed to understand the impact of standard nutritional interventions addressing malnutrition in pediatric dilated cardiomyopathy. Additionally, understanding the impact of lifestyle modification on pediatric dilated cardiomyopathy patients who are obese may be helpful in management of these patients as well possibly contributing to a better understanding of the obesity paradox in adult heart failure.



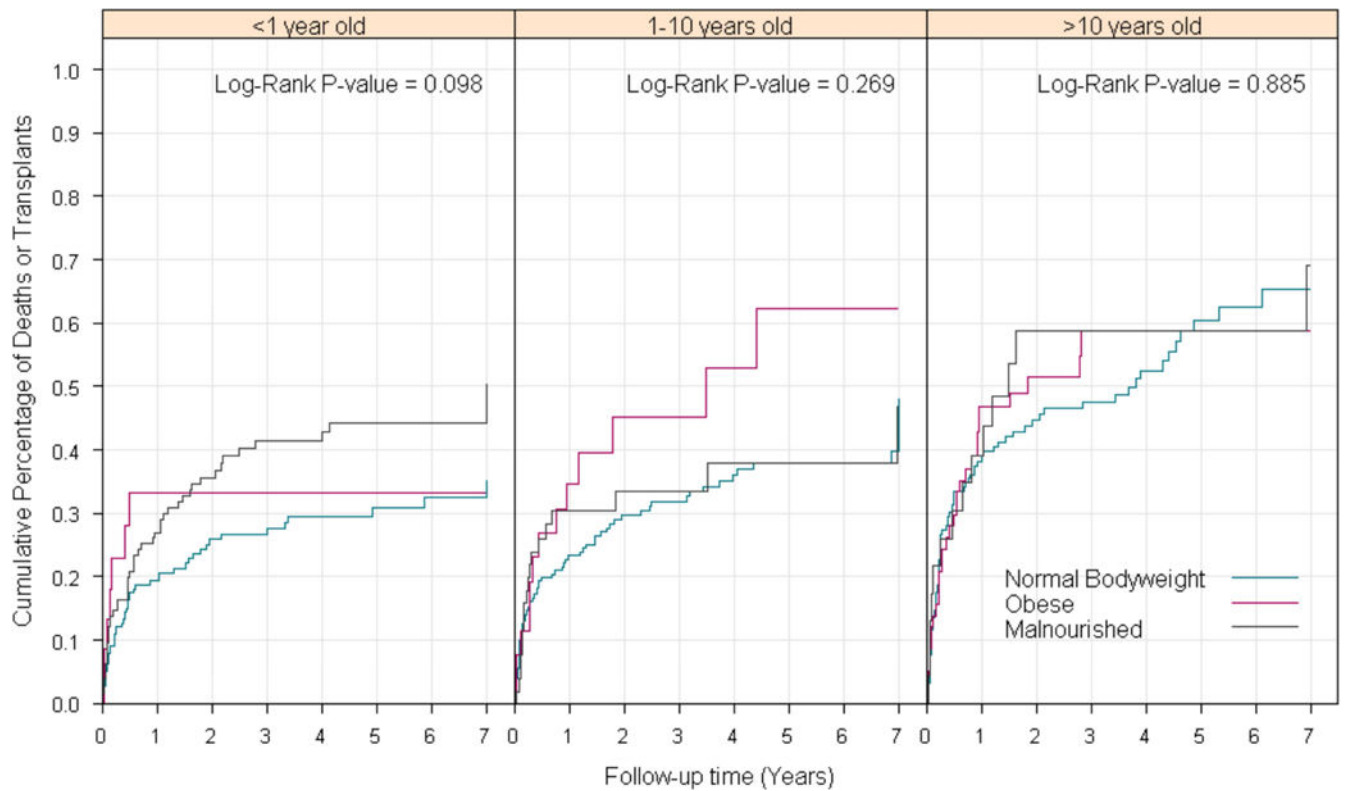
**Figure 1A.**  
Cumulative incidence of death stratified by nutrition group.



**Figure 1B.** Cumulative incidence of death or transplant stratified by nutrition group. MN = malnourished; NB = normal bodyweight



**Figure 2.** Competing outcomes analysis for patients by nutrition group for years 1 through 7. There was increased risk of mortality in MN patients compared to NB ( $p=0.030$ ), however, no difference between obese and NB ( $p=0.223$ ). There were no significant differences between groups in transplant rate ( $p=0.401$ ).



**Figure 3.**

Cumulative incidence of death or transplant or last date of contact by nutrition group stratified by age group. Values are right-censored at seven years.

Number of patients in each category: <1 year old: Total=345; Malnourished =131; Normal Bodyweight =187; Obese =27; 1-10 years old: Total =300; Malnourished =58; Normal Bodyweight= 214; Obese =28; >10 years old: Total =259; Malnourished =25; Normal Bodyweight = 169; Obese =65.



**Table 1**

Patient Characteristics by Nutrition Group

Characteristic Mean (±SD) or N (%)	Bodyweight				P-Value <sup>#</sup>
	Malnourished (N=214)	Normal Bodyweight (N=570)	Obese (N=120)	Overall	
Age at Diagnosis (years), mean±SD	2.70±4.50	5.70±5.95	9.00±6.34	<0.001	<0.001
Gender (male)	101 (47.2%)	293 (51.4%)	72 (60%)	0.080	<0.001
Height-for-age z-score	0.27±1.98	-0.20±1.44	-0.67±2.77	<0.001	0.010
Weight-for-age z-score	-1.77±1.75	-0.29±1.24	1.81±2.21	<0.001	<0.001
BMI	13.25±1.49	17.13±3.10	29.90±13.20	<0.001	<0.001
Race				0.832	
White	127 (59.9%)	328 (58.8%)	58 (48.7%)		
Black	42 (19.8%)	108 (19.4%)	39 (32.8%)		
Hispanic	23 (10.8%)	89 (15.9%)	16 (13.4%)		
Other	22 (10.2%)	45 (5.9%)	7 (5.0%)		
Etiology				0.164	
Idiopathic	174 (81.3%)	441 (77.5%)	100 (83.3%)		
Myocarditis	29 (13.6%)	97 (17.0%)	9 (7.5%)		
Familial	11 (5.1%)	31 (5.4%)	11 (9.2%)		
Family History of Cardiomyopathy*	27 (21.1%)	80 (23.5%)	26 (36.1%)	<b>0.044</b>	0.595
Family History of Sudden Death	12 (8.9%)	44 (13.1%)	13 (17.1%)	0.207	
HF at Diagnosis	171 (79.9%)	396 (69.7%)	81 (68.6%)	<b>0.012</b>	0.813
Anti-heart Failure Therapy	193 (91.0%)	476 (85.6%)	99 (83.2%)	0.072	0.028

\* Family history is defined in this Registry as any family member with a known cardiomyopathy and captured separately from familial dilated cardiomyopathy, which is defined as genetic cause of cardiomyopathy. SD-standard deviation, BMI-body mass index, FamHx-family history, HF-heart failure.

<sup>#</sup> Pair-wise comparison P values <0.017 are considered statistically significant, applying post hoc Bonferroni correction

**Table 2**

Echocardiographic Characteristics by Nutrition Group

Characteristic Mean (±SD) or N (%)	Bodyweight			Overall	P-Value <sup>#</sup>		
	Malnourished (N=214)	Normal Bodyweight (N=570)	Obese (N=120)		Malnourished vs. Normal	Normal vs. Obese	Malnourished vs. Obese
Left Ventricular Dimensions, mean±SD							
LV EDD* z-score	5.32±2.40	4.19±2.53	3.44±2.52	<0.001	<0.001	0.004	<0.001
LV ESD <sup>†</sup> z-score	7.00±2.92	5.79±2.80	5.02±2.91	<0.001	<0.001	0.014	<0.001
LV EDPT <sup>‡</sup> z-score	-0.20±3.09	-0.56±2.45	-0.92±2.19	0.097			
LV EDST <sup>§</sup> z-score	-0.62±3.09	-0.87±1.81	-1.12±1.72	0.156			
Ratio of LV EDPT/EDD	0.14±0.16	0.13±0.04	0.14±0.05	0.660			
Ratio of LV EDST/EDD z-score	-1.02±7.55	-1.35±2.35	-1.15±2.32	0.685			
Functional Assessment							
LV Fractional Shortening z-score	-9.29±4.15	-8.01±3.77	-7.64±3.39	<0.001	<0.001	0.363	<0.001
Mitral Regurgitation	70 (79.5%)	146 (68.9%)	25 (73.5%)	0.169			
Left Atrial Dilatation	38 (43.7%)	66 (31.4%)	10 (30.3%)	0.113			

\* LV-EDD- left ventricle end diastolic dimension

<sup>†</sup> LV-ESD- left ventricle end systolic dimension

<sup>‡</sup> LV-EDPT- left ventricle end diastolic posterior wall thickness

<sup>§§</sup> LV-EDST- left ventricle end diastolic septal thickness

<sup>#</sup> Pair-wise comparison P values <0.017 are considered statistically significant, applying post hoc Bonferroni correction

**Hazard Ratios<sup>1</sup> Modeling Time to Death, Time to Transplant, and Time to Death or Transplant by Nutritional Group<sup>2</sup>, HR (95%CI)**

**Table 3**

	<b>Normal</b>	<b>Malnourished</b>	<b>Obese</b>	<b>p-value</b>
Death	1.00 (referent)	2.06 (1.17, 3.65)	1.49 (0.72, 3.08)	0.042
Death or Transplant	1.00 (referent)	1.18 (0.84, 1.67)	1.03 (0.69, 1.54)	0.630
Transplant	1.00 (referent)	0.89 (0.57, 1.38)	0.87 (0.54, 1.40)	0.758