Association of Body Mass Index with Patient-Centered Outcomes in Children with ESRD

Elaine Ku,*[†] David V. Glidden,[‡] Chi-yuan Hsu,* Anthony A. Portale,[†] Barbara Grimes,[‡] and Kirsten L. Johansen*

*Division of Nephrology, Department of Medicine, [†]Division of Pediatric Nephrology, Department of Pediatrics, and [‡]Department of Biostatistics and Epidemiology, University of California, San Francisco, California

ABSTRACT

Obesity is associated with less access to transplantation among adults with ESRD. To examine the association between body mass index at ESRD onset and survival and transplantation in children, we performed a retrospective analysis of children ages 2–19 years old beginning RRT from 1995 to 2011 using the US Renal Data System. Among 13,172 children, prevalence of obesity increased from 14% to 18%, whereas prevalence of underweight decreased from 12% to 9% during this period. Over a median follow-up of 7.0 years, 10,004 children had at least one kidney transplant, and 1675 deaths occurred. Risk of death was higher in obese (hazard ratio [HR], 1.17; 95% confidence interval [95% CI], 1.03 to 1.32) and underweight (HR, 1.26; 95% CI, 1.09 to 1.47) children than children with normal body mass indices. Obese and underweight children were less likely to receive a kidney transplant (HR, 0.92; 95% CI, 0.87 to 0.97; HR, 0.83; 95% CI, 0.78 to 0.89, respectively). Obese children had lower odds of receiving a living donor transplant (odds ratio, 0.85; 95% CI, 0.74 to 0.98) if the transplant occurred within 18 months of ESRD onset. Adjustment for transplant in a time–dependent Cox model attenuated the higher risk of death in obese but not underweight children (HR, 1.09; 95% CI, 0.96 to 1.24). Lower rates of kidney transplantation may, therefore, mediate the higher risk of death in obese children with ESRD. The increasing prevalence of obesity among children starting RRT may impede kidney transplantation, especially from living donors.

The prevalence of obesity has been increasing in adults and children over the last two decades in the United States.[1] In adults with ESRD, obesity has increased at rates that have exceeded those of the general population.[2,3] Because poor appetite and growth failure are commonly observed in children with CKD, obesity may be perceived more favorably than malnutrition by providers and families, which may have led to an increase in body mass index (BMI) in children with CKD over time.[4–6]

Although obesity is consistently associated with better survival among adults on hemodialysis, it is possible that obese children with ESRD have higher mortality risk compared with children with normal BMI for several reasons. First, children who are already obese at ESRD onset may gain even more weight post-transplant with steroid exposure and therefore, be at higher risk for subsequent cardiovascular morbidity and mortality. Second, childhood obesity is associated with lower familial socioeconomic status and African-American race, both of which have been associated with lower rates of transplantation.[7–11] Because the majority of children with ESRD are treated with transplantation and transplantation improves survival in children with ESRD, obese children may, therefore, experience higher mortality risk. Third, many

Correspondence: Dr. Elaine Ku, Division of Nephrology, University of California, San Francisco, 521 Parnassus Avenue, C443, Box 0532, San Francisco, CA 94143-0532. Email: elaine.ku@ucsf.edu

transplant centers have adopted policies that restrict kidney donation by individuals with BMI above varying thresholds.[12] It is conceivable that children with high BMI could have less access to living related adult donors, who may also be obese and have obesity-associated comorbidities (hypertension or diabetes) that would preclude donation, especially because obesity frequently clusters within families.[7,13–15] For example, in one study that examined factors limiting live kidney donation from parents to children with CKD, up to 74% of parental donors who were willing to donate were deemed unsuitable for medical reasons, the majority of which were related to hypertension, diabetes, and/or obesity.[7]

In this study, we used the US Renal Data System (USRDS) to examine temporal trends in BMI at the time of first treatment for ESRD in the United States pediatric population over the last two decades and examine the association between BMI at initial ESRD onset and outcomes. We hypothesized that BMI has increased and that obese children would have higher risk of mortality mediated, at least in part, by less transplantation.

RESULTS

Study Cohort

We identified 13,172 children with nonmissing BMI at the time of initial treatment for ESRD in the USRDS. Median age was 14.5 years old (interquartile range [IQR] =10.5–17.5), 55% were boys, 67% were Caucasian, and 46% received Medicaid at the time of ESRD onset (Table 1). Median neighborhood income was $47,801 in this cohort, excluding patients with missing zip codes ($n=14$) and erroneous zip codes that could not be correlated with a neighborhood median household income ($n=394$). Mean chronological age– and sex–standardized BMI z score at time of initial RRT was 0.21 (SD±1.45) on the basis of the Centers for Disease Control and Prevention (CDC) standards for United States children. Mean BMI z score using height-age at the time of initial RRT was 0.48 (SD± 1.42). Mean BMI z score using the World Health Organization (WHO) standards was 0.41 (SD±1.61). Overall, 10% of children were underweight, and 17% of children were obese. Children <5 years old had the highest prevalence of obesity (25%) versus children between 5 and 13 years of age (15%) or children 13 years of age and older (18%; $P<0.001$). By BMI category, children who were obese were more likely to be African American, have lower socioeconomic status (by neighborhood median income and Medicaid status), and have GN or hypertension as cause of their ESRD (Supplemental Table 1). Median GFR at the start of RRT was 7.4 ml/min per 1.73 m^2 (IQR=5.4–10.0) and did not differ by BMI category (Supplemental Table 1).

Temporal Trends in BMI

Between 1995 and 1999, 14% of children were obese at time of initial RRT, but between 2000 and 2009, 18% of children were obese. We observed a parallel decrease in the percentage of underweight children (from 12% between 1995 and 1999 to 9% between 2000 and 2009). In adjusted analyses, every later 5-calendar year interval was associated with a 0.10-unit higher average BMI z score (95% confidence interval [95% CI], 0.08 to 0.13; $P<0.001$). Results were similar using BMI z scores on the basis of height-age (0.09-unit increase; 95% CI, 0.06 to 0.11 for every 5-year interval) and slightly higher using the WHO age– and sex–standardized z scores (0.12-unit increase; 95% CI, 0.09 to 0.15 for every 5-year interval).

Association between BMI and Death

Approximately 13% of the cohort ($n=1675$) died during 97,884 person-years of follow-up (median follow-up period =7.0 years; IQR=3.5–10.9). The risk of death was 1.17 times higher in children who were obese (95% CI, 1.03 to 1.32; $P=0.02$) compared with children with normal BMI (Table 2). As expected, underweight children also had a higher risk of death (hazard ratio [HR], 1.26; 95% CI, 1.09 to 1.47; $P=0.003$). No significant interactions between BMI category and initial dialysis modality (hemodialysis versus peritoneal dialysis), race, or cause of ESRD were noted (all $P>0.10$). In sensitivity analysis, additional adjustment for median income in Cox models of death yielded similar results (Table 2). The proportion of cardiovascular causes of death in children with a nonmissing cause of death ($n=1322$; 79%) was similar among underweight children (31%), children with normal BMI (32%), and obese children (29%; $P=0.37$).

We repeated our adjusted Cox model analysis using height-age and the WHO standardized z scores and found similar results (Supplemental Table 2).

Association between BMI and Transplant Outcomes

Approximately three quarters of individuals ($n=10,004$) received at least one kidney transplant, and preemptive transplants occurred in 15% of the cohort (Figure 1).

Compared with children with normal BMI, obese children were less likely to receive a kidney transplant (HR, 0.92; 95% CI, 0.87 to 0.97; $P=0.004$) overall (Table 3) but did not have lower odds of receiving a preemptive transplant (odds ratio [OR], 1.14; 95% CI, 0.99 to 1.32; $P=0.06$). Underweight children also were less likely to receive a kidney transplant overall (HR, 0.83; 95% CI, 0.78 to 0.89; $P<0.001$), including having lower odds of preemptive transplant (OR, 0.58; 95% CI, 0.47 to 0.70; $P<0.001$). Among children treated with dialysis as initial RRT, the risk of transplant in the adjusted Cox model was 0.88 for obese children (95% CI, 0.82 to 0.93; $P<0.001$) and 0.89 for underweight children (95% CI, 0.83 to 0.96; $P=0.003$). In secondary analysis with additional adjustment for median income, results were similar (Table 3). Use of Fine–Gray models to account for the competing risk of death yielded similar results (data not shown). Use of height-age and the WHO standardized BMI z scores also yielded similar results (Supplemental Table 3).

To further explore differences in transplantation rates by BMI category, we assessed the risk of living versus deceased donor transplant within the first 18 months after ESRD onset.

Table 1. Characteristics of children at the time of initial treatment of ESRD

Characteristics at ESRD Onset (n=13,172)	Percentage (N)
Median age, yr [IQR]	14.5 [10.5–17.5]
Age category, yr	
2–5	7 (902)
>5–13	29 (3857)
>13	64 (8413)
Race	
Caucasian	67 (8785)
African American	24 (3140)
Asian	6 (777)
Native American	2 (211)
Other	2 (259)
Boys	55 (7216)
Cause of ESRD	
Congenital/cystic/hereditary diseases/ pyelonephritis/interstitial nephritis	38 (5061)
GN (primary and secondary)	25 (3322)
FSGS	15 (1991)
Hypertension	4 (546)
Other	17 (2252)
Median GFR (ml/min per 1.73 m²) at ESRD onset[a] [IQR]	7.4 [5.4–10.0]
Medicaid	46 (6063)
Height <5th percentile overall	31 (4068)
Initial treatment modality[b]	
Transplantation	15 (2004)
Hemodialysis	52 (6821)
Peritoneal dialysis	32 (4199)
Living donor source for transplant[c]	47 (4653)

[a]Missing in n=2304 because of missing serum creatinine values, especially in patients with preemptive transplantation.
[b]Missing exact dialysis modality (hemodialysis versus peritoneal) in n=148.
[c]Missing in n=48.

In total, 6732 transplants (67% of all initial transplants) occurred within the first 18 months of ESRD onset. Those who were obese had lower odds of receiving a living versus deceased donor transplant compared with those who had normal BMI (OR, 0.85; 95% CI, 0.74 to 0.98; P=0.03), whereas underweight children were not less likely to receive a living donor transplant than children with normal BMI (Table 3). In sensitivity analysis, we repeated this multivariate logistic regression model using a 12- and 24-month timeframe for transplantation after ESRD onset and found similar trends at both extremes of BMI (Table 3). Additional adjustment for median income yielded similar results.

In sensitivity analysis, use of BMI *z* scores on the basis of height-age yielded similar results. Obese and underweight children had lower odds of living donor transplant, although for obese children, the difference did not achieve statistical significance at 18 months after additional adjustment for median income (Supplemental Table 3). Use of the WHO standardized BMI *z* scores yielded similar results for odds of living donor transplant as our primary analysis using the CDC BMI *z* scores.

Association between BMI, Transplantation, and Mortality

To evaluate whether differences in rates of kidney transplantation may have mediated the higher risk of death in obese children, we included receipt of a transplant as a time-dependent covariate in our Cox model of risk of death. In this model, there were 58,786 at-risk person-years with a functional allograft and 39,098 at-risk person-years on dialysis. The risk of death in children who were obese (HR, 1.09; 95% CI, 0.96 to 1.24; P=0.16) was attenuated after adjustment for the lower transplant rate among obese children, but the risk of death in underweight children remained similar (HR, 1.20; 95% CI, 1.03 to 1.39; P=0.02) and was not attenuated by adjustment for transplant (Table 2). In sensitivity analysis using the WHO standardized BMI *z* scores, results were similar. However, in analysis using height-age BMI *z* scores, the higher risk of death in obese children was only partially attenuated by adjustment for transplant as a time-dependent covariate (Supplemental Table 2).

In exploratory analysis, we also evaluated the risk of death by BMI category during the 39,098 person-years of follow-up

Table 2. Cox model for risk of death by BMI category in children

Model	Underweight		Obese	
	HR[a] (95% CI)	P Value	HR[a] (95% CI)	P Value
Unadjusted (n=13,172)	1.27 (1.09 to 1.47)	0.002	1.23 (1.09 to 1.39)	0.001
Adjusted model in primary analysis (n=13,172)	1.26 (1.09 to 1.47)	0.003	1.17 (1.03 to 1.32)	0.02
Model with additional adjustment for median income (n=12,764)	1.35 (1.16 to 1.58)	<0.001	1.15 (1.01 to 1.31)	0.04
Adjusted for transplant as a time-dependent covariate (n=13,172)	1.20 (1.03 to 1.39)	0.02	1.09 (0.96 to 1.24)	0.16

All models were adjusted for sex, race, cause of ESRD, Medicaid status, and calendar year of ESRD onset and stratified by age categories to protect against nonproportionality.
[a]Normal BMI is the reference category, with underweight defined as <5th percentile and obese defined as ≥95th percentile using the CDC age– and sex–standardized BMI *z* scores
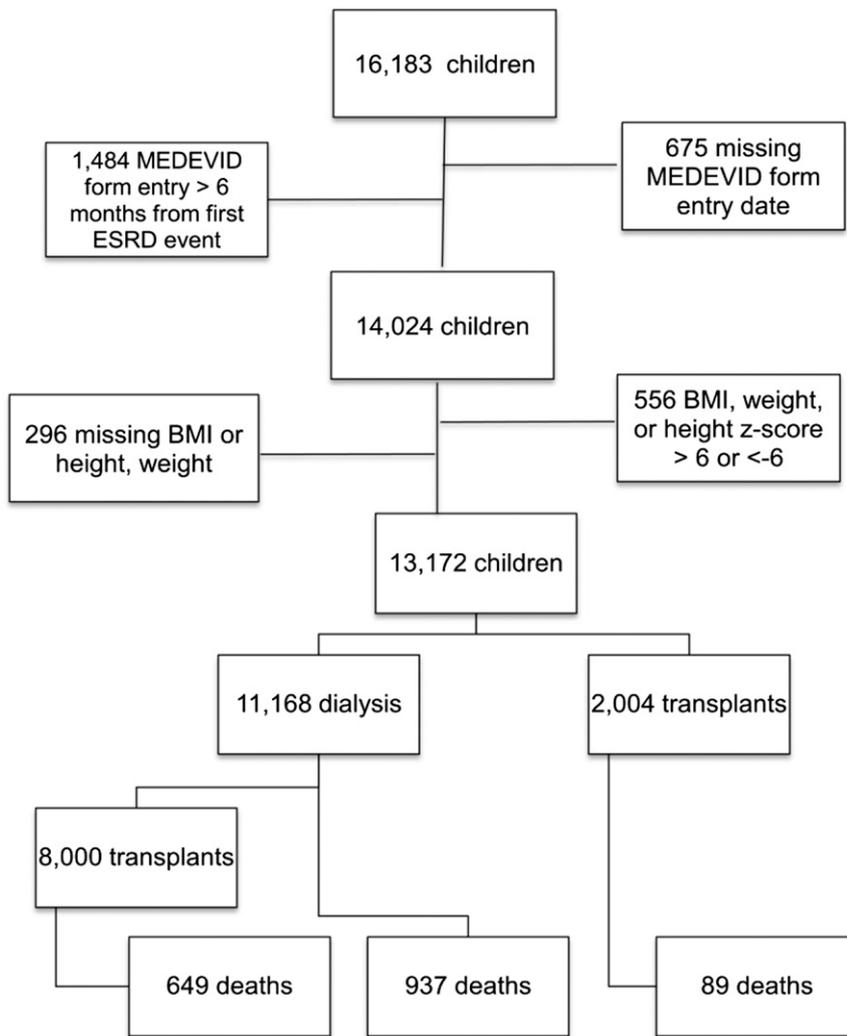
Figure 1. Cohort profile. Flow diagram of outcomes in children according to the USRDS between 1995 and 2012.

confounders, including demographic characteristics, cause of ESRD, socioeconomic status (as indicated by Medicaid status and median neighborhood income), and calendar year. The higher risk of death in obese children was attenuated by adjustment for transplant as a time-dependent covariate, suggesting that lower likelihood of kidney transplant may mediate the higher mortality risk of children with ESRD.

The higher risk of death in the underweight pediatric population may be secondary to malnutrition or illness severity and is not surprising. In contrast, the U-shaped association between BMI and risk of death in our study, with a higher risk of death also at higher BMI, differs from observed associations among adults on hemodialysis, in which high BMI is associated with lower risk of death.[20–22] This observation may be attributable, in part, to the higher prevalence of kidney transplantation in children compared with adults, although in exploratory analysis, we did not find a lower risk of death in obese children on dialysis.

Our results are consistent with a prior study that included children treated with dialysis and transplantation, which also reported a higher risk of death among obese and underweight children.[23] However, there was no overall survival difference between obese and nonobese recipients of kidney transplants on basis of pretransplant BMI in a study using data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS).[9] Of note, NAPRTCS collects data voluntarily reported by participating North American transplant centers. NAPRTCS focused initially on children undergoing kidney transplantation, and the report by Hanevold *et al.*[9] did not include children treated with dialysis.[24] In contrast, our study includes a more contemporary cohort of children from the USRDS (a database that receives data reported for all patients in the United States with ESRD, including dialysis and transplant). Taken together, the results from prior published studies are consistent with our analyses, suggesting that there is a survival disadvantage among obese children with ESRD that is mediated, at least in part, by lower rates of transplantation. Even with adjustment for known factors associated with lower transplantation rates, including African-American race and low socioeconomic status, the association between BMI and mortality risk persisted in our study.

Although disparities in kidney transplantation rates may partially mediate the higher risk of death, we also hypothesized

attributed to dialysis. Risk of death in this analysis was higher for underweight children (HR, 1.20; 95% CI, 1.01 to 1.42; *P*=0.03) but not for obese children (HR, 1.09; 95% CI, 0.95 to 1.26; *P*=0.20) compared with normal weight children.

DISCUSSION

We found a significant increase in the prevalence of obesity at initial ESRD onset in pediatric patients from 14% in 1995–1999 to 18% in 2005–2009, which mirrors trends in the general pediatric population.[16,17] There was a U-shaped association between extremes of BMI and death among children beginning RRT. Compared with children with normal BMI, obese children were less likely to receive a kidney transplant and less likely to receive a kidney transplant from a living donor, which is the preferred source because of superior graft and patient survival.[18,19] The lower likelihood of kidney transplant in obese children persisted even after adjustment for potential

Table 3. Regression models for risk of transplant starting from ESRD onset

Model	Underweight		Obese	
	HR[c] or OR[c] (95% CI)	P Value	HR[c] or OR[c] (95% CI)	P Value
Outcome of Cox proportional hazards model[a]				
Receipt of transplant at any time during follow-up (n=13,172)	0.83 (0.78 to 0.89)	<0.001	0.92 (0.87 to 0.97)	0.004
Receipt of transplant at any time during follow-up with additional adjustment for median income (n=12,764)	0.83 (0.77 to 0.88)	<0.001	0.92 (0.87 to 0.98)	<0.01
Receipt of transplant if dialysis was the initial treatment modality (n=11,168)	0.89 (0.83 to 0.96)	0.003	0.88 (0.82 to 0.93)	<0.001
Outcome of logistic regression model[b]				
Preemptive transplant (n=13,172)	0.58 (0.47 to 0.70)	<0.001	1.14 (0.99 to 1.32)	0.06
Living donor transplant within 18 mo of ESRD onset (n=6732)	0.98 (0.82 to 1.18)	0.87	0.85 (0.74 to 0.98)	0.02
Living donor transplant within 18 mo of ESRD onset with additional adjustment for median income (n=6521)	0.97 (0.80 to 1.16)	0.73	0.85 (0.73 to 0.98)	0.03
Living donor transplant within 12 mo of ESRD onset (n=5448)	1.04 (0.84 to 1.28)	0.73	0.91 (0.77 to 1.06)	0.23
Living donor transplant within 24 mo after ESRD onset (n=7582)	0.92 (0.78 to 1.09)	0.34	0.86 (0.75 to 0.98)	0.03

[a]Adjusted for sex, race, cause of ESRD, Medicaid status, and calendar year of ESRD onset and stratified by age categories.
[b]Adjusted for age category at incident ESRD, sex, race, cause of ESRD, Medicaid status, and calendar year of ESRD onset.
[c]Normal BMI is the reference category, with underweight defined as <5th percentile and obese defined as ≥95th percentile using the CDC age– and sex–standardized BMI z scores.

that obesity increases the risk of cardiovascular mortality in children with ESRD. Mortality of children with ESRD is 30 times higher than that of the general pediatric population, and cardiovascular disease remains a leading cause of death.[25] However, we did not find an excess risk of cardiovascular death in obese compared with underweight or normal weight children, although >20% of causes of death were missing in the USRDS database. The 7-year median follow-up period may not have been long enough to capture long–term cardiovascular risk, especially because mortality with graft function has declined in pediatric recipients of kidney transplants over the last few decades.[19]

Our study could not address the reasons for the lower rate of transplantation and lower odds of receiving a living related transplant among obese children. A recent study of adults with ESRD also found that obese patients were less likely to receive kidney transplants, particularly from living donors.[26] The Amsterdam Forum on the Care of the Live Kidney Donor published guidelines in 2005 that discourage kidney donation if donor BMI is >35 kg/m^2, although transplant centers in the United States are allowed to use clinical discretion to set center-specific criteria for donor eligibility.[27] A little over one half of United States transplant centers cap donor BMI at 35 kg/m^2, and approximately 10% have an even lower threshold of 30 kg/m^2.[12,28] Given the known correlation between children's and parents' BMIs, a potential explanation for the low rate of transplantation among obese children is that their parents are less likely to be accepted as living donors.[14] Because parents account for almost 80% of living kidney donors for children, any limitation in parental donation could have an important effect.[29] Limited access to kidney transplantation could, in turn, affect survival, because kidney transplantation offers the best long–term survival for children with ESRD.[30]

However, we could not test this hypothesis directly, because we lack information on whether, how often, or why donors were excluded.

The strengths of our study include the large size of the national cohort, the contemporary nature of the data, and a relatively large number of outcomes (including deaths and transplants). Limitations include the observational nature of the data, potential errors in data used for BMI determination, lack of data on immunosuppression regimens and longitudinal changes in allograft function or BMI, and missing data from Kidney Transplant Registration or Centers for Medicare and Medicaid (CMS)-2728 forms, which may have caused some misclassification of BMI category and transplant status and excluded some children from our study. However, any bias introduced by these problems would likely be toward the null. Although severe edema may be less common among children than adults with advanced CKD because of higher prevalence of polyuria in congenital anomalies of the kidney and urinary tract,[31] it should be noted that we had no way of adjusting BMI values for the potential presence of fluid overload. However, although this is a recognized limitation of BMI in the CKD population, there is still a strong correlation between BMI and body fat in this population.[32] Our selection of a relatively high BMI cutoff to define obesity should ensure that these patients also have relatively high fat mass, even if our primary analysis may underestimate BMI z scores on the basis of chronological age. We found similar, if not stronger, associations with clinical outcomes in obese children using BMI z scores on the basis of height-age.

Although the proportion of underweight children starting RRT decreased over time, possibly as a result of better recognition of nutritional needs in children with kidney disease, it is alarming that the prevalence of obesity among

children has increased, especially given our findings of lower kidney transplantation rates and higher risk of death among obese children. In light of the high mortality risk of children with kidney disease, it may be important for all providers who care for these patients to monitor closely for obesity as well as malnutrition. Additional studies should explore the potential inequities in access to kidney transplantation related to body size in pediatric recipients.

CONCISE METHODS

Study Population and Data Source
We performed a retrospective cohort study of children between the ages of 2 and 19 years old who developed ESRD between January 1, 1995, and December 31, 2011 using data from the USRDS, the national ESRD registry. Children under the age of 2 years old were excluded, because BMI standards are not available for this age group from the CDC.[33] Patient demographic characteristics (age at incident ESRD, sex, and race), cause of ESRD, Medicaid coverage (yes/no as an indicator of lower income status), zip code, date of ESRD onset, height and weight, and BMI at incident ESRD were abstracted from the CMS-2728 Medical Evidence (MEDEVID) Form and patients' files in the USRDS. Zip code was used to determine median household income of patients' neighborhood using median income values from the American Community Survey between 2006 and 2010.[34] Initial ESRD treatment modality (transplant versus dialysis) was determined at the first ESRD service date as listed in the MEDEVID file. eGFR was determined by the equation by Schwartz et al.[35] using serum creatinine and height reported on the CMS-2728 form at the time of ESRD onset.

BMI Ascertainment
Weight and height at incident ESRD were used to determine BMI in kilograms per square meter of height, or BMI reported on the MEDEVID form was used if weight or height was missing. BMI z score on the basis of chronological age was chosen as a measure of obesity because of its ease of use in clinical practice and availability within the USRDS database in our primary analysis. All BMI values were age and sex standardized to BMI z scores using the 2000 CDC standards for United States children.[36] We defined underweight as BMI<5th percentile for age (corresponding to z score <−1.64) and obese as BMI≥95th percentile for age (corresponding to z score ≥1.64) according to the CDC criteria.[34,36,37] We purposely selected a high cutoff for our definition of obesity and classified children who would qualify as overweight by the CDC criteria (BMI≥85th percentile) as normal weight status to allow for potential fluid overload, which may result in misclassification of weight status and BMI category.

We included only children with initial onset of ESRD, which was defined by availability of a CMS-2728 MEDEVID form filed within 6 months of the first ESRD service date (n=14,024). Forms with missing BMI and unavailable height and weight were excluded (n=296). Children with extremes of BMI, weight, or height z scores >6 or <−6 were excluded from analysis (n=556), because we considered these scores likely to be erroneous (Figure 1).

In sensitivity analysis, we also redefined BMI z scores on the basis of height-age (defined as the approximate age when a child's observed height would be at the 50th percentile for height using the CDC standards) rather than chronological age to account for delayed maturation in children with CKD.[32,38] Because BMI standards for children are defined between ages 2 and 19 years old, heights-ages for <2 years of age were reset to 2 years of age and height-ages for >18 years of age were reset to 18.5 years of age to derive corresponding BMI z scores. Finally, we also re-expressed BMI z scores using the WHO age– and sex–standardized standards and definitions of underweight (BMI z score <−2) and obese (BMI z score >2) in additional sensitivity analyses.[39,40] BMI z scores >6 or <−6 (n=75) on the basis of the WHO standards were excluded from analysis, because we considered these to be likely erroneous.

Outcome Ascertainment
We determined transplant dates and donor source (living versus deceased) for first transplant using the USRDS patient and transplant files, which contain data reported by transplant centers to the United Network for Organ Sharing. We abstracted death dates and primary causes of death (cardiovascular, a major cause of death in children with ESRD, versus other) from the USRDS patients file. We ascertained outcomes (death and transplants) through June 30, 2012.

Statistical Analyses
Temporal Trends in BMI
We examined temporal trends in BMI at incident ESRD using a multivariable linear regression model with calendar year of ESRD onset as the main predictor and BMI z score at ESRD onset as the outcome. This model was adjusted for demographic factors, including age at ESRD onset, sex, race, cause of ESRD, Medicaid status, and calendar year of ESRD onset. In sensitivity analysis, we repeated our adjusted model using height-age and the WHO age– and sex–standardized BMI z scores.

Association between BMI and Risk of Death
We assessed the association between BMI category at initial ESRD onset and risk for all-cause mortality using a Cox proportional hazards model adjusted for sex, race, cause of ESRD, Medicaid status, and calendar year (to account for temporal changes in BMI at incident ESRD over time and any potential secular trends in survival) and stratified for age category at initial ESRD onset. We categorized age at ESRD onset as 2–5, >5 but <13, and ≥13 years old to protect against potential nonproportionality in mortality risk, because prior studies have shown differences in mortality risk by age.[23,41,42] We did not censor patients at the time of transplantation given that transplantation improves survival and relates to our primary outcome of all-cause mortality.

We performed sensitivity analysis using adjusted Cox models for risk of death as the outcome and BMI z scores on the basis of height-age and the WHO age– and sex–standardized BMI z scores as primary predictors.

Association between BMI and Transplantation
We assessed the association between BMI category (underweight or obese versus normal) at initial ESRD onset and risk for kidney transplant

using a Cox proportional hazards model adjusted for sex, race, cause of ESRD, Medicaid status, and calendar year and stratified for age category at incident ESRD to protect against nonproportionality. If transplantation was the initial ESRD treatment modality without any preceding dialysis, we set transplant to occur at 0.5 days after ESRD onset to capture these events in our Cox model. We did not adjust for blood type or histocompatibility, because we deemed such characteristics unlikely to be associated with our primary predictor (BMI category). We also examined the odds of receiving a preemptive transplant according to BMI category using a logistic regression model adjusted for demographic characteristics (age category at incident ESRD, sex, and race), cause of ESRD, Medicaid status, and calendar year. Deaths occurring before kidney transplantation were censored in our primary analysis, although in sensitivity analysis, we used Fine–Gray models to account for death as a competing risk.

To further explore potential differences in risk of kidney transplantation, we used a multivariable logistic regression model to assess the odds of a living versus a deceased donor transplant in those who received a first transplant within the first 18 months of ESRD onset using BMI categories as our main predictor and adjusting for the same covariates as in prior models. We selected 18 months as a reasonable time period for living donor kidney transplantation to occur, accounting for the time needed to identify and work up potential living donors and optimize the clinical status of patients in preparation for elective transplant. Prior data have also shown that the majority of living and deceased donor kidney transplants occur within this timeframe.[43,44]

In sensitivity analysis, we assessed the association between BMI category and transplantation in adjusted Cox models (as described above) but included only patients who received dialysis as initial RRT. We also repeated the analysis including individuals who received their first transplant within 12 and 24 months of ESRD onset. Because of the number of missing or erroneous zip codes in our data ($n=414$), we adjusted only for Medicaid status as an indicator of socioeconomic status in our primary analyses; in sensitivity analyses, we further adjusted for median neighborhood income in all models using the subset of patients with available income data. Finally, all adjusted Cox models for risk of transplant and logistic regression models for odds of living versus deceased donor transplant were repeated using height-age and the WHO standardized BMI z scores in sensitivity analyses.

Association between BMI, Transplantation, and Mortality
To examine whether the association between BMI category at incident ESRD and risk of death was potentially mediated by transplantation, we used the same multivariable Cox proportional hazards model and further adjusted for transplant as a time-dependent covariate. This mediation analysis was repeated using height-age and the WHO standardized BMI z scores in sensitivity analyses. In exploratory analysis, we also examined the risk of death during the follow-up duration by BMI category in our time–dependent Cox model.

With the exception of conversion of BMI, weight, and height into standardized BMI z scores, which was performed using a Statistical Analysis System tool provided by the CDC,[37] all data analyses were conducted in Stata 13. The WHO age– and sex–standardized z scores were derived using an online STATA tool provided by the WHO.[40]

The Committee on Human Research of the University of California San Francisco considers this work not to be human subjects research.

DISCLOSURES
None.

REFERENCES

1. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM: Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA* 291: 2847–2850, 2004
2. Kramer HJ, Saranathan A, Luke A, Durazo-Arvizu RA, Guichan C, Hou S, Cooper R: Increasing body mass index and obesity in the incident ESRD population. *J Am Soc Nephrol* 17: 1453–1459, 2006
3. Stenvinkel P, Zoccali C, Ikizler TA: Obesity in CKD—what should nephrologists know? *J Am Soc Nephrol* 24: 1727–1736, 2013
4. Sienna JL, Saqan R, Teh JC, Frieling ML, Secker D, Cornelius V, Geary DF: Body size in children with chronic kidney disease after gastrostomy tube feeding. *Pediatr Nephrol* 25: 2115–2121, 2010
5. Foster BJ, McCauley L, Mak RH: Nutrition in infants and very young children with chronic kidney disease. *Pediatr Nephrol* 27: 1427–1439, 2012
6. Han SH, Han DS: Nutrition in patients on peritoneal dialysis. *Nat Rev Nephrol* 8: 163–175, 2012
7. Hidalgo G, Tejani C, Clayton R, Clements P, Distant D, Vyas S, Baqi N, Singh A: Factors limiting the rate of living-related kidney donation to children in an inner city setting. *Pediatr Transplant* 5: 419–424, 2001
8. Keane E, Layte R, Harrington J, Kearney PM, Perry IJ: Measured parental weight status and familial socio-economic status correlates with childhood overweight and obesity at age 9. *PLoS ONE* 7: e43503, 2012
9. Hanevold CD, Ho PL, Talley L, Mitsnefes MM: Obesity and renal transplant outcome: A report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatrics* 115: 352–356, 2005
10. Mohan S, Mutell R, Patzer RE, Holt J, Cohen D, McClellan W: Kidney transplantation and the intensity of poverty in the contiguous United States. *Transplantation* 98: 640–645, 2014
11. Murasko JE: Trends in the associations between family income, height and body mass index in US children and adolescents: 1971-1980 and 1999-2008. *Ann Hum Biol* 38: 290–306, 2011

12. Mandelbrot DA, Pavlakis M, Danovitch GM, Johnson SR, Karp SJ, Khwaja K, Hanto DW, Rodrigue JR: The medical evaluation of living kidney donors: A survey of US transplant centers. *Am J Transplant* 7: 2333–2343, 2007

13. Krebs NF, Jacobson MS; American Academy of Pediatrics Committee on Nutrition: Prevention of pediatric overweight and obesity. *Pediatrics* 112: 424–430, 2003

14. Vester U, Schaefer A, Kranz B, Wingen AM, Nadalin S, Paul A, Malagò M, Broelsch CE, Hoyer PF: Development of growth and body mass index after pediatric renal transplantation. *Pediatr Transplant* 9: 445–449, 2005

15. Birch LL, Fisher JO: Development of eating behaviors among children and adolescents. *Pediatrics* 101: 539–549, 1998

16. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM: Prevalence of high body mass index in US children and adolescents, 2007-2008. *JAMA* 303: 242–249, 2010

17. Ogden CL, Carroll MD, Kit BK, Flegal KM: Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA* 307: 483–490, 2012

18. Van Arendonk KJ, James NT, Orandi BJ, Garonzik-Wang JM, Smith JM, Colombani PM, Segev DL: Order of donor type in pediatric kidney transplant recipients requiring retransplantation. *Transplantation* 96: 487–493, 2013

19. Laskin BL, Mitsnefes MM, Dahhou M, Zhang X, Foster BJ: The mortality risk with graft function has decreased among children receiving a first kidney transplant in the United States. *Kidney Int* 87: 575–583, 2015

20. Johansen KL, Young B, Kaysen GA, Chertow GM: Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr* 80: 324–332, 2004

21. Kalantar-Zadeh K, Streja E, Kovesdy CP, Oreopoulos A, Noori N, Jing J, Nissenson AR, Krishnan M, Kopple JD, Mehrotra R, Anker SD: The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. *Mayo Clin Proc* 85: 991–1001, 2010

22. Park J, Ahmadi SF, Streja E, Molnar MZ, Flegal KM, Gillen D, Kovesdy CP, Kalantar-Zadeh K: Obesity paradox in end-stage kidney disease patients. *Prog Cardiovasc Dis* 56: 415–425, 2014

23. Wong CS, Gipson DS, Gillen DL, Emerson S, Koepsell T, Sherrard DJ, Watkins SL, Stehman-Breen C: Anthropometric measures and risk of death in children with end-stage renal disease. *Am J Kidney Dis* 36: 811–819, 2000

24. NAPRTCS Online. North American Pediatric Renal Trials and Collaborative Studies. Available at: https://web.emmes.com/study/ped/. Accessed March 10, 2015

25. Mitsnefes MM: Cardiovascular disease in children with chronic kidney disease. *J Am Soc Nephrol* 23: 578–585, 2012

26. Segev DL, Simpkins CE, Thompson RE, Locke JE, Warren DS, Montgomery RA: Obesity impacts access to kidney transplantation. *J Am Soc Nephrol* 19: 349–355, 2008

27. Delmonico F; Council of the Transplantation Society: A report of the amsterdam forum on the care of the live kidney donor: Data and medical guidelines. *Transplantation* 79[Suppl]: S53–S66, 2005

28. Yandell K: Transplant centers struggle with donor obesity. *New York Times*, 2012. Available at: http://well.blogs.nytimes.com/2012/08/06/transplant-centers-struggle-with-donors-obesity/?_r=0. Accessed November 10, 2014

29. The EMMES Corporation: *NAPRTCS Annual Transplant Report*, 2010. Available at: https://web.emmes.com/study/ped/annlrept/2010_Report.pdf. Accessed December 5, 2014

30. Warady BA, Neu AM, Schaefer F: Optimal care of the infant, child, and adolescent on dialysis: 2014 update. *Am J Kidney Dis* 64: 128–142, 2014

31. Ghane Sharbaf F, Bitzan M, Szymanski KM, Bell LE, Gupta I, Tchervenkov J, Capolicchio JP: Native nephrectomy prior to pediatric kidney transplantation: Biological and clinical aspects. *Pediatr Nephrol* 27: 1179–1188, 2012

32. Gao T, Leonard MB, Zemel B, Kalkwarf HJ, Foster BJ: Interpretation of body mass index in children with CKD. *Clin J Am Soc Nephrol* 7: 558–564, 2012

33. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL: 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics. *Vital Health Stat 11* 246: 1–190, 2002

34. Center MPS: *Zip Code Characteristics: Mean and Median Household Income*, University of Michigan, Institute for Social Research, 2010. Available at: http://www.psc.isr.umich.edu/dis/census/Features/tract2zip/index.html. Accessed September 5, 2014

35. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL: New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 20: 629–637, 2009

36. Center for Disease Control: Healthy weight - it's not a diet, it's a lifestyle, 2014. Available at: http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html. Accessed March 3, 2014

37. Centers for Disease Control and Prevention: A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years), 2014. Available at: http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed March 30, 2014

38. KDOQI Work Group: 2008 update. Executive summary. *Am J Kidney Dis* 53[Suppl 2]: S11–S104, 2009

39. WHO: *WHO Child Growth Standards*, WHO, Geneva, Switzerland, 2014. Available at: http://www.who.int/childgrowth/standards/bmi_for_age/en/. Accessed March 1, 2015

40. WHO: *WHO Anthro (Version 3.2.2) and Macros*, WHO, Geneva, Switzerland, 2011. Available at: http://www.who.int/childgrowth/software/en/. Accessed February 26, 2015

41. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ: Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990-2010. *JAMA* 309: 1921–1929, 2013

42. Andreoni KA, Forbes R, Andreoni RM, Phillips G, Stewart H, Ferris M: Age-related kidney transplant outcomes: Health disparities amplified in adolescence. *JAMA Intern Med* 173: 1524–1532, 2013

43. Patzer RE, Sayed BA, Kutner N, McClellan WM, Amaral S: Racial and ethnic differences in pediatric access to preemptive kidney transplantation in the United States. *Am J Transplant* 13: 1769–1781, 2013

44. Reese PP, Hwang H, Potluri V, Abt PL, Shults J, Amaral S: Geographic determinants of access to pediatric deceased donor kidney transplantation. *J Am Soc Nephrol* 25: 827–835, 2014

<u>Supplementary Table 1:</u> **Characteristics of children at ESRD onset by BMI category**

Characteristics at ESRD onset	Underweight (N=1294)	Normal BMI (N= 9596)	Obese (N=2282)
Median age (years) *[IQR]	15.5 [11.5-17.5]	14.5 [10.5-17.5]	14.5 [10.5-17.5]
*Age category**			
2-5 years old	7 (86)	6 (587)	10 (229)
>5-13 years	25 (325)	31 (2,961)	25 (571)
>13 years	68 (883)	63 (6,048)	65 (1,482)
*Race**			
Caucasian	66 (855)	68 (6,558)	60 (1,372)
African American	22 (286)	22 (2,138)	31 (716)
Asian	8 (106)	6 (566)	5 (105)
Native American	0.8 (10)	2 (156)	2 (45)
Other	3 (37)	2 (178)	2 (44)
Male	56 (722)	55 (5,244)	55 (1,250)
*Cause of ESRD**			
Congenital/cystic/ hereditary diseases/pyelonephritis/ interstitial nephritis	44 (573)	39 (3,775)	31 (713)
Glomerulonephritis	21 (271)	26 (2,490)	25 (561)
Focal segmental glomerulosclerosis	12 (150)	14 (1,351)	21 (490)
Hypertension	4 (46)	4 (352)	7 (148)
GFR at ESRD onset[1] (mL/min/1.73 m^2) [IQR]	7.4 [5.5-10.1]	7.4 [5.4-9.9]	7.6 [5.6.-10.2]
*Medicaid**	46 (589)	46 (4,366)	49 (1,108)
*Median income by zip code[2]**	$48,768	$48,193	$45,732
*Height <5th percentile overall**	35 (449)	31 (2,963)	29 (656)
*Living donor source for transplant[3]**	48 (453)	47 (3527)	42 (673)

* Statistically significantly different by BMI category, p < 0.05
[1]Missing in N=2,304 due to missing serum creatinine values, especially in patients with preemptive transplantation
[2]Missing in N=408
[3]Missing in N=48

Supplementary Table 2: Cox model[1] for risk of death by BMI category in children in sensitivity analyses

	Underweight	Obese
Height-age BMI Model[2]	**Hazard ratio* (95% CI)**	
Unadjusted (N=13,172)	1.25 (1.05-1.49)	1.33 (1.19-1.49)
Adjusted model in primary analysis (N=13,172)	1.21 (1.01-1.45)	1.28 (1.14-1.43)
Model with additional adjustment for median income (N=12,764)	1.28 (1.07-1.53)	1.26 (1.12-1.41)
Adjusted for transplant as a time-dependent covariate (N=13,172)	1.19 (0.99-1.42)	1.18 (1.06-1.33)
WHO BMI Model[3]	**Hazard ratio* (95% CI)**	
Unadjusted (N=13,097)	1.43 (1.21-1.69)	1.34 (1.16-1.56)
Adjusted model in primary analysis (N=13,097)	1.44 (1.21-1.70)	1.28 (1.10-1.50)
Model with additional adjustment for median income (N=12,693)	1.54 (1.30-1.82)	1.26 (1.08-1.48)
Adjusted for transplant as a time-dependent covariate (N=13,097)	1.44 (1.21-1.73)	1.10 (0.97-1.25)

[1] All models were adjusted for sex, race, cause of ESRD, Medicaid status, and calendar year of ESRD onset, and stratified by age categories to protect against non-proportionality

[2] Normal BMI is reference category with underweight defined as <5th percentile and obese defined as ≥ 95th percentile using CDC sex-standardized BMI z-score standards based on height-age

[3] Normal BMI is reference category with underweight defined as BMI z-score < -2 and obese defined as BMI z-score >2 using WHO age- and sex-standardized BMI z-score standards and chronological age (N=75 further excluded due to implausible BMI z-scores <-6 or >6).

Supplementary Table 3: Regression models for transplant outcomes using height-age and WHO standardized BMI z-scores.

	Underweight	Obese
Outcome of Cox proportional hazards model using height-age standardized BMI[1]	**Hazard ratio* (95% CI)**	
Receipt of transplant at any time during follow-up (N=13,172)	0.90 (0.83-0.97)	0.88 (0.84-0.93)
Receipt of transplant at any time during follow-up with additional adjustment for median income (N=12,764)	0.89 (0.82-0.96)	0.88 (0.83-0.92)
Receipt of transplant if dialysis was initial treatment modality (N=11,168)	0.96 (0.88-1.04)	0.84 (0.80-0.89)
Outcome of Cox proportional hazards model using WHO standardized BMI[1]	**Hazard ratio* (95% CI)**	
Receipt of transplant at any time during follow-up (N=13,097)	0.82 (0.75-0.89)	0.89 (0.83-0.95)
Receipt of transplant at any time during follow-up with additional adjustment for median income (N=12,693)	0.81 (0.75-0.88)	0.89 (0.83-0.96)
Receipt of transplant if dialysis was initial treatment modality (N=11,101)	0.87 (0.80-0.95)	0.82 (0.76-0.89)
Outcome of logistic regression model using height-age standardized BMI[2]	**Odds ratio* (95% CI)**	
Preemptive transplant (N=13,172)	0.64 (0.51-0.80)	1.08 (0.94-1.23)
Living donor transplant within 18 months of ESRD onset (N=6,732)	0.98 (0.80-1.21)	0.87 (0.77-0.99)
Living donor transplant within 18 months of ESRD onset with additional adjustment for median income (N=6,521)	1.01 (0.81-1.24)	0.88 (0.77-1.01)
Living donor transplant within 12 months of ESRD onset (N=5,448)	1.05 (0.82-1.33)	0.91 (0.78-1.05)
Living donor transplant within 24 months after ESRD onset (N=7,582)	0.94 (0.77-1.14)	0.89 (0.79-1.00)
Outcome of logistic regression model using WHO standardized BMI[2]	**Odds ratio* (95% CI)**	
Preemptive transplant (N=13,097)	0.57 (0.45-0.72)	1.19 (1.00-1.43)
Living donor transplant within 18 months of ESRD onset (N=6,697)	1.07 (0.87-1.33)	0.79 (0.65-0.94)
Living donor transplant within 18 months of ESRD onset with additional adjustment for median income (N=6,492)	1.07 (0.85-1.33)	0.77 (0.64-0.93)
Living donor transplant within 12 months of ESRD onset (N=5,421)	1.17 (0.91-1.52)	0.81 (0.66-0.99)
Living donor transplant within 24 months after ESRD onset (N=7,544)	1.01 (0.82-1.23)	0.82 (0.69-0.97)

[1] Adjusted for sex, race, cause of ESRD, Medicaid status, and calendar year of ESRD onset and stratified by age categories

[2] Adjusted for age category at incident ESRD, sex, race, cause of ESRD, Medicaid status, calendar year of ESRD onset