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Body mass Index and Survival: The Association Between Increased BMI and Kidney Transplant Survival

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Emory University
Master of Science in Public Health
2017

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A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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By Kristen Senetar

The need for kidney transplants is on the rise due to an increase in chronic health conditions that result in kidney failure. However, kidneys are a very scarce resource and transplants are costly. Therefore, factors associated with improved long-term transplant success must be identified and integrated into future transplant policy, including indicators for transplant priority. Body mass index (BMI) has been widely used as a determining factor for individuals being placed on the transplant list. However, the use of BMI is controversial because the current literature suggests conflicting relationship between an increased BMI value at time of transplant and decreased long-term survival. Thus, what is needed is a study that analyzes a large nationally representative database to help determine if higher BMI values at time of transplant significantly decrease long-term transplant success. Contrary to current clinical practice, it is hypothesized that an increased BMI at time of transplant will have no association with decreased long-term survival following a kidney transplant. Findings from this study will help influence future transplant policy by providing evidence for whether or not BMI should be a factor in kidney transplant decisions.

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Chapter 1: Introduction

Background

The first successful kidney transplant occurred in 1954.[1] Since then, the number of successful organ transplants has grown tremendously. Unfortunately, the wait list for receiving a transplant has also grown. According to the National Kidney Foundation, the average wait time for a kidney transplant is more than three years.[2] As a result, 13 people die every day while on the waiting list.[3] In 2015 alone, fewer than 18,000 kidney transplants occurred, while the number of individuals on the waitlist to receive a kidney exceeded 99,000.[4] It is crucial that long-term success rates following kidney transplants remain high given the fact that organs are a scarce resource and that the average kidney transplant in the United States costs more than $330,000.[5]

Current Study

This study examines the relationship between recipient body mass index (BMI) at time of kidney transplant and long-term transplant success. If higher BMI values at time of transplant are shown to have a negative impact on patient survival via an increase in the probability of transplant failure, then transplant centers could require overweight and obese patients to lose weight as a condition of being placed on the wait list. This could save the healthcare system money by increasing survival rates and, ultimately, establishing a more efficient and successful distribution of donor organs.

Previous Studies

A transplant recipient's BMI at the time of transplant may play an important role in long-term transplant success since some studies have found that obese patients (BMI >= 30) have worse survival outcomes. However, other studies have found that the impact of BMI is small or non-existent. Thus, additional large-scale studies are needed. Due to differences in lifestyle and medical care between countries, it is best for a study to use data on US transplants only so that the results will be applicable to US transplant policies.

Chapter 2: Literature Review

End Stage Renal Disease

End stage renal disease (ESRD) occurs when an individual's kidneys no longer function well enough to support their body and is most often the result of diabetes or hypertension.[6-9] Individuals with ESRD must remain on dialysis indefinitely, creating large financial, social and personal burdens on these patients and their families.[10] For instance, the time commitments and side-effects associated with dialysis often cause individuals to lose or involuntarily reduce their workload, which can be detrimental to themselves and to society.[11] Individuals spending a majority of their day at the dialysis clinic might lack the energy to work, potentially resulting in a lower quality of life and financial hardships for the individual and reduced workforce for society.

Transplantation by the numbers

According to the United Network for Organ Sharing (UNOS) database, more than 120,000 people are currently waiting for an organ transplant in the United States and more than 100,000 of those individuals are waiting for a kidney.[12, 13] Unfortunately, the number of living donations continues to decline.[14] As a result, more than half of all individuals over the age of 60 who are currently on the organ donation waitlist will die before receiving a deceased donor organ.[15] Furthermore, more than 29 million Americans currently have Type 2 diabetes, one of the leading causes of end stage renal disease and, ultimately, a risk factor for eventually needing a kidney transplant.[16] With this number on the rise, it is likely that the demand for organs will only continue to increase in the future.[17]

Costs

Although they carry high upfront costs, transplants have the potential to be less costly than keeping an individual on long-term dialysis. The average cost of a single kidney transplant in the United States is more than $330,000.[18] Medicare spends about $17,000 per year to support transplant patients, while the annual cost for supporting a patient on dialysis is more than $72,000.[19] Individuals with ESRD account for only 1% of the Medicare population, yet they account for nearly 7% of Medicare spending each year.[20] This places a sizable financial burden on the US healthcare system and, combined with the limited supply of organs, makes long-term success of kidney transplantation crucial. By identifying ways to decrease the number of individuals who return to dialysis following a transplant failure, this study could help decrease the burden on the healthcare and payer systems.

Transplant Care and Outcomes

Following a transplant, patients must take immunosuppressive medications to prevent graft failure for the remaining life of their transplanted organ.[21] These medications can cost as much as $14,000 per year.[22] For individuals who are on Medicare only because of ESRD and a subsequent kidney transplant, coverage ends three years post-transplant.[23] If individuals do not have another source of insurance after this three year mark, the high cost of the immunosuppressant medications may cause some them to stop or decrease their medication, leading them to re-enter ESRD due to organ rejection, which could result in requiring a second transplant.[24] Even if individuals follow their prescribed medication regimen, they are not guaranteed a successful transplant outcome due to additional risks, such as infection.[25]

Follow-up medication is not the only concern regarding kidney transplants. Individual-level factors at time of transplant, such as BMI, are also important because they are modifiable. BMI is a widely used measure of a combination of an individual's weight and height and it may have a relationship to kidney transplant outcomes.[26] Although there is controversy surrounding the accuracy of BMI, it is an important factor for analysis due to its modifiability.[27] While BMI affects health, an individual's health can also affect their BMI. Individuals who are very sick may present with very low BMI values. Replying solely on BMI could result in an incorrect assessment of their health.[28]

Body Mass Index

Body mass index, which is calculated using an individual's weight and height, serves as a general indicator of body fatness.[29] Among individuals receiving kidney transplants, BMI is of particular interest because its modifiable nature and established relationship to patient outcomes during dialysis.[30, 31] If BMI were directly associated with less favorable kidney transplant outcomes, transplant centers could consider adding a more holistic approach to patient care and increase attention to diet and lifestyle choices. Although BMI is usually associated with poorer health outcomes, obese patients on dialysis actually have better outcomes in terms of survival while on dialysis.[32, 33] This is contradictory to what is generally expected because higher BMI values are usually associated with lower overall health and an increased risk for chronic conditions such as hypertension and Type 2 diabetes.[34] As kidney transplant recipients are usually on dialysis prior to receiving their transplant, this paradox is of special interest.

Current Literature

Numerous retrospective data analysis studies have looked at BMI in relation to kidney transplant outcomes.[35-38] Most studies have placed primary focus on the extreme BMI categories, such as individuals who are classified as morbidly obese, rather than individuals in the overweight BMI category. Many of these studies have found that survival rates are lower among obese patients. Using the Netherlands Organ Transplantation Registry (NOTR) database, one study found that patients with a BMI of at least 30 kg/m^2 at the time of their transplant had a lower rate of survival at both one and five years post-transplant compared to individuals with a

BMI of less than 30 kg/m^2 at time of transplant (94% vs. 97% at one year follow-up and 81% vs. 89% at 5 year follow-up).[39] Another study involving 376 patients also found that, compared to non-obese recipients, obese kidney transplant recipients had lower one and three year survival rates.[40]

However, several retrospective studies have found that, at 5 years post-transplant, obese patients and non-obese patients have no statistically significant difference in survival.[41, 42] A systematic review of 17 additional studies supported the same finding.[43] Therefore, the literature regarding the impact of obesity on kidney transplant outcomes remains uncertain. As a result, the current literature may have little impact on transplant policies due to its ambiguity.

To further explore the relationship between BMI and kidney transplantation outcomes, studies have also examined obesity in relation to decreased graft function, which occurs when the transplanted kidney does not work as well as expected.[44] Like those looking at patient survival, these studies provide conflicting results. Based on data from the United Network for Organ Sharing (UNOS) for individuals who received a transplant between 1997 and 1999, one retrospective study found that obese patients experienced an increase risk for delayed graft function.[45] Similar results were seen in a study using UNOS data from 2004 to 2009.[46] A study using data from the NOTR found similar results for graft survival at one a five years post-transplant.[47] Furthermore, a literature review found numerous studies stating that obese individuals had worse graft survival outcomes in followups ranging from one to five years following the transplant.[48] Finally, a single-center observational study from 2000 to 2010 also found that individuals with a BMI of at least 30 kg/m^2 were more likely to experience delayed graft function than non-obese individuals.[49]

Current literature provides little clarity as to the nature of the relationship between BMI and graft function. Several single-center studies found that there was no association between obesity and an increased incidence of delayed graft function.[50, 51] Overall, it is clear that the current literature needs to be strengthened with studies conducted on large, US data sets from the most recent years in an attempt to have the most accurate analysis of current transplant outcomes.

While there is a general consensus that being obese is beneficial to individuals on dialysis, there currently is no agreed-upon relationship between higher BMI values and graft function or long-term patient survival following a kidney transplant. The current study will strengthen the literature surrounding this relationship and potentially resolve the currently disputing literature. This study will utilize a large data set containing data from individuals who received a single kidney transplant in the United States. This is unique in that many of the previous studies were conducted using smaller data sets or non-US data. Furthermore, most current literature focuses on the extremes in BMI values. The analyses are focused on obese or morbidly obese individuals, rather than individuals who are classified as being overweight. This lack of focus on other BMI groups, such as the underweight and overweight categories, leaves a gap in current literature that needs to be filled in order to gain a more complete understanding of BMI and its role in organ transplantation success. By using a large data set from within the United States and by including all BMI groups, but focusing on those who are overweight, this gap will be narrowed. Narrowing this gap will allow transplant programs to make more informed decisions regarding where they should place cut-off values for kidney transplant recipients with a goal of increasing long-term kidney transplant success. Based on the size and design of previous studies, it is hypothesized that there will be no difference in long-term survival of kidney transplant recipients, measured by kidney transplant failure, based on BMI value at time of transplant.

By strengthening the current literature with an additional large study using US data, there is potential to influence health policy as a means of increase long-term patient survival following a kidney transplant.

Chapter 3: Methods

Sample

The Emory University IRB has approved this study. This study includes individuals from the Scientific Registry of Transplant Recipients (SRTR) database (1990 to 2014) who have received a kidney transplant. In order to be included in the study population, individuals were 18 years or older at the time that they were placed on the transplant waiting list. In addition, they must have valid/non-missing values for their transplant date and BMI at time of transplant. If any of these data points are missing, the individual was excluded from analysis.

Measures

Based on Andersen's framework and the economic theory of demand, the following individual-level constructs confound the focal relationship of BMI and long-term transplant success.[52, 53]

Characteristics of age, race/ethnicity and gender are believed to be demographic confounding factors.[54] While there is limited literature on which to draw, it is possible that as individuals' age, their ability to stay physically active declines, which would result in higher BMI values or lower overall health.[55] Therefore, there is a positive hypothesized relationship between BMI and age. Additionally, older individuals may have additional risk factors relating to their health compared to younger, healthier individuals. Therefore, there is a hypothesized negative relationship between age and long-term transplant success.

According to current literature, men are slightly more likely than women to experience kidney transplant success.[56] Therefore, the hypothesized relationship between gender (female) and long-term kidney transplant success is negative. As for BMI, men, on average, have a slightly higher BMI value than women.[57, 58] Therefore, there is a negative relationship hypothesized between gender and BMI.

Current literature shows that African Americans have lower rates of long-term success following a kidney transplant than White individuals.[59] As a result, it is hypothesized that race (White) will have a positive association with long-term kidney transplant success. White individuals also tend to have lower BMI values compared to non-white individuals, so there is a hypothesized negative relationship between race/ethnicity and BMI.[60]

Enabling confounders for this framework include educational attainment, type of insurance (public, private, etc.) and the year in which the transplant occured. Private health insurance has been shown to be associated with a decrease in transplant failure.[61] Economic theory supports this because private insurance would likely lower the out-of-pocket costs to patients for immunosuppressant medication, therefore increasing demand for them from the privately insured transplant patients. Access to these medications is a major barrier to continued transplant success. By lowering or removing this barrier, privately insured individuals should be more likely to have a successful transplant outcome. Therefore, there is a positive hypothesized relationship between private health insurance and long-term kidney transplant outcome. There is insufficient literature to hypothesize a relationship between insurance type and BMI category.

The second enabling confounder is education. Higher levels of education (college and above) have been shown to be associated with improved kidney transplant outcomes.[62, 63] As a result, with some college experience as a reference, there is a hypothesized positive relationship between education and long-term kidney transplant success. Furthermore, some evidence suggests that individuals with more education have lower rates of obesity.[64] Therefore, there is a hypothesized negative relationship between education and BMI.

The final enabling confounder is the year in which the kidney transplant occurred. It is hypothesized that later years would result in increased survival rates due to general improvements and advances made in medicine over time. Therefore, there is a hypothesized positive relationship between year of transplant and the focal dependent variable.

Health status is considered a need confounder in this analysis. The diabetes variable provided in the data set will serve as an indicator for health status. Current studies suggest that there is no longer a negative association between an individual having diabetes and a decrease in transplant success.[65] Therefore, there is a negative relationship hypothesized between comorbidities and the focal dependent variable. Literature does support a relationship between diabetes and higher BMI values. [66] Therefore, there is a hypothesized positive relationship between comorbidities and the focal independent variable of BMI at time of transplant.

Family structure/support, mental health status, income, socioeconomic status (SES) and living location (rural, urban, etc.) are all unmeasured constructs in the framework. Family structure/support refers to factors such as an individual's living situation. Mental health status is an important factor in relation to kidney transplant success. Illnesses such as depression have been associated with decrease graft survival in transplant patients.[67] Living in an urban location might make it easier for individuals to gain access to pharmacies and other medical needs through public transportation options.[68, 69] While income is an important factor for analysis, it is unmeasured in the data set directly. Furthermore, potential indicator variables for SES, such as working for income, are scarcely populated, resulting in inadequate data for analysis.

Construct Measurement

Body Mass Index (BMI): The focal independent variable of BMI was provided in the dataset and was included only if it had valid and non-missing values. BMI was measured using the guidelines provided by the Centers for Disease Control (CDC). The BMI variable for each individual at the time of transplant was categorized into one of the following groups: underweight (BMI < 18.5), normal weight (BMI 18.5 – 24.9), overweight (BMI 25.0-29.9) or obese (BMI >= 30.0).[70]

Long-term Transplant Success: The construct of long-term transplant success was measured by the occurrence of transplant failure, patient death or patient lost to follow-up. This information is provided in the follow-up data for each transplant recipient in the data set. In order to allow for the largest study cohort, follow-up data for a maximum of 15 years post-transplant will be used for the analysis.

Age: Age was recorded for each individual at the time that they were placed on the transplant waiting list. This continuous variable will be used at a single time point (the time at which the individual was placed on the kidney transplant waiting list).

Race/ethnicity: Race/ethnicity was recorded in the data set using two separate variables for each individual at the time they were added to the transplant list. The first variable, race, included the following groupings: missing, White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Arab or Middle Eastern, Indian Sub-continent, Unknown, Hispanic/Latino and Multi-Racial. For simplicity and to reach larger cell numbers, these will be condensed into the following five categories: White, Black/African American, Hispanic/Latino, Asian and Other/Unknown.

Gender: The gender construct will be measured using the gender variable provided in the data set. The variable is dichotomous, with options for male and female.

Education: Education was recorded in the dataset using the following seven categories: none, grade school (0-8), high school (9-12) or GED, attended college/technical school, associate/bachelor degree, post-college graduate degree and unknown. The analysis will be done using these provided groupings for education.

Insurance: The construct of insurance will be measured by using the insurance variable provided in the dataset at the time of transplant. The categories in the dataset are private insurance, public insurance – Medicaid, public insurance – Medicare FFS, public insurance – Medicare and choice, public insurance – CHIP, public insurance Department of VA, public insurance – other government, self, donation, free care, pending, foreign government, public insurance – Medicare unspecified, US/State government agency and unknown. For simplicity, these categories will be condensed into the following five groups: private, Medicare, Medicaid, other/unknown and other government insurance.

Health status: The construct of health status will be measured by the diabetes indicator variable. This indicator will be categorical for either yes, no or unknown. The data set lacked additional health status indicator variables. Since diabetes often coincides with additional chronic conditions such as hypertension, it will be used as an indicator variable in this study for health status.[71]

Research Design

The analysis includes the kidney transplant standard analytical file (SAF) from the Scientific Registry of Transplant Recipients (SRTR) and covers individuals who received kidney transplant during multiple years (1990-2013), allowing for the creation of a larger dataset once inclusion and exclusion criteria are applied.[72] Some of the information included in the dataset includes medical history, transplant date, physical activity level, post-transplant information and insurance type.

The SRTR provides a compilation of data collected by the Organ Procurement and Transplantation Network (OPTN) regarding all individuals involved in solid organ transplants of a heart, lung, kidney, pancreas, liver or intestine (donors and recipients) within the United States since 1989.[73] There is no response rate provided because transplant professionals collect and report this data electronically, usually at the time of patient office visits.[74] Other sources, like the Centers for Medicare and Medicaid Services, provide some additional data that is added to the SRTR data, resulting in the SAF. The kidney transplant SAF can be linked on an individual-level to other SRTR data sets, including the transplant candidate file, donor data and the transplant follow-up data set, which is completed six months post-transplant, one year post-transplant and then each year for as long as the individual is living and not lost to follow-up.[75] The only general inclusion criteria for the SAF are that individuals are organ donors or recipients of organ transplants within the US.

Data Analysis

The sample was analyzed using SAS 9.3. The sample included individuals who were 18 years or older at the time of being placed on the transplant waiting list and were recipients of a kidney transplant between January 1, 1990 and January 26, 2013. Individuals with missing BMI values at time of transplant were removed from the data set. Lost-to-follow-up was used in censoring the follow-up period for each patient. If an individual died, the date in which the death was indicated was used as the last follow-up date. If a transplant failure was recorded, this date was used as the last follow-up date. Additionally, if an individual was lost to follow-up, their last recorded visit date was used to determine length of follow-up post-transplant. For any patients who had follow-up data for more than 15 years post-transplant, only the first 15 years were included in the analysis. The outcome of interest (long-term transplant survival) was determined by the absence of both graft failure and patient death within the maximum 15-year post-transplant follow-up period. The hypothesis that BMI is not negatively associated with long-term kidney transplant success was tested using a survival analysis.

A Cox proportional hazard test was conducted on the analytic sample, providing adjusted hazard ratios. The model was adjusted for race/ethnicity, education, gender, insurance, diabetes, age at listing and transplant year.

Conceptual Framework

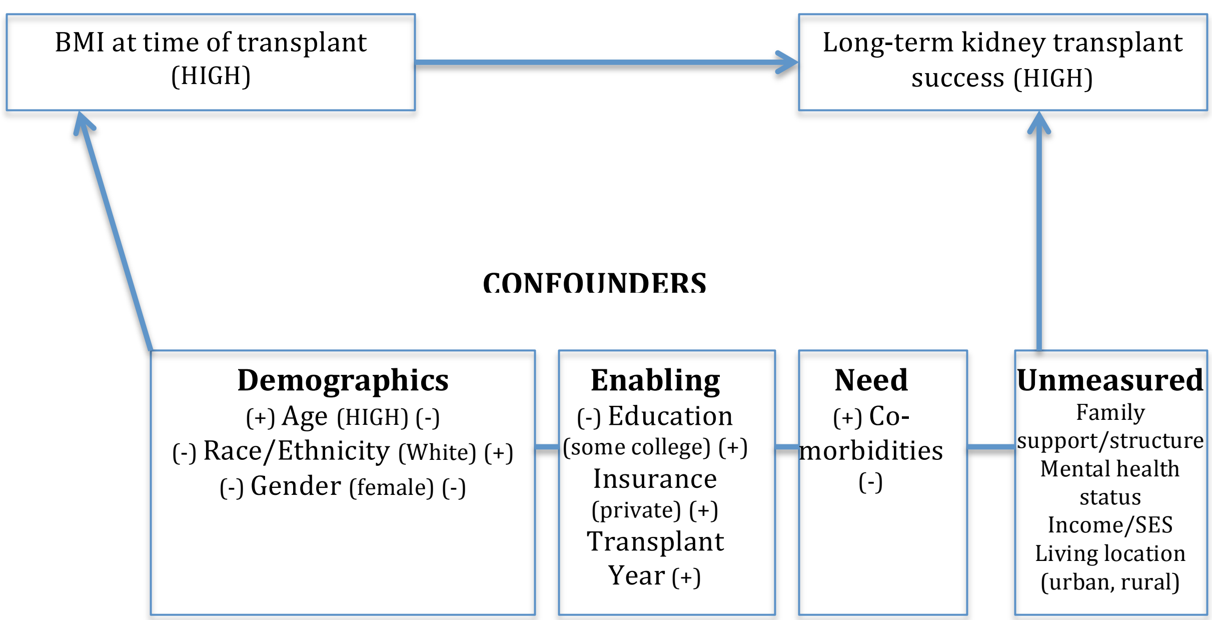

Figure 1. Conceptual Framework: The figure shows the conceptual framework used for this study, based on the Andersen framework. The focal relationship is between BMI at time of kidney transplant and long-term transplant success.

Chapter 4: Results

Introduction

The analysis included 205,411 individuals who received a kidney transplant in the US between January 1, 1990 and January 23, 2013. These individuals had valid BMI values at the time of transplant and were at least 18 years old when they were placed on the transplant waiting list.

Descriptive Statistics

Table 1. Descriptive Statistics This table gives the general descriptive statistics regarding the study population.

	TOTAL (%)	Underweight (%)	Normal (%)	Overweight (%)	Obese (%)
N (%)	205,411	6,759 (3.3)	75,447 (36.7)	67,687 (33.0)	55,518 (27.0)
Average BMI	27	17	22	27	35
Average Age at Listing	47	40	45	49	49
Gender					
Female	81,459 (39.6)	4,065 (60.1)	31,430 (41.7)	22,754 (33.6)	23,210 (41.8)
Male	123,952 (60.4)	2,694 (39.9)	44,017 (58.3)	44,933 (66.4)	32,308 (58.2)
Race/Ethnicity					
White	113,951 (55.5)	3,772 (55.8)	42,532 (56.4)	37,503 (55.4)	30,144 (54.3)
Black/African American	52,271 (25.4)	1,389 (20.6)	16,770 (22.2)	17,290 (25.5)	16,822 (30.3)
Hispanic/Latino	26,008 (12.7)	788 (11.7)	9,573 (12.7)	9,133 (13.5)	6,514 (11.7)
Asian	9,991 (4.9)	715 (10.6)	5,498 (7.3)	2,709 (4.0)	1,069 (1.9)
Other/Unknown	3,190 (1.6)	95 (1.4)	1,074 (1.4)	1,052 (1.6)	969 (1.7)
Insurance					
Private	85,411 (41.6)	2,269 (33.6)	28,642 (38.0)	28,978 (42.8)	25,522 (46.0)
Medicare	74,944 (36.5)	2,199 (32.5)	26,065 (34.5)	25,164 (37.2)	21,516 (38.8)
Medicaid	10,893 (5.3)	461 (6.8)	4,360 (5.8)	3,302 (4.9)	2,770 (5.0)
Other/Unknown	31,270 (15.2)	1,765 (26.1)	15,395 (20.4)	9,190 (13.6)	4,920 (8.9)
Other Gov. Insurance	2,893 (1.4)	65 (1.0)	985 (1.3)	1,053 (1.6)	790 (1.4)
Education					
Less than HS	8,591 (4.2)	214 (3.2)	2,869 (3.8)	3,244 (4.8)	2,264 (4.1)
HS/GED	66,680 (32.5)	1,835 (27.1)	22,369 (29.6)	22,126 (32.7)	20,350 (36.7)
Some College	37,302 (18.2)	1,060 (15.7)	12,674 (16.8)	12,314 (18,2)	11,254 (20.3)
College Degree	24,278 (11.8)	751 (11.1)	8,576 (11.4)	8,117 (12.0)	6,834 (12.3)
Grad Degree	10,135 (4.9)	244 (3.6)	3,610 (4.8)	3,570 (5.3)	2,711 (4.9)
None/Unknown	58,425 (28.4)	2,655 (39.3)	25,349 (33.6)	18,316 (27.1)	12,105 (21.8)

Table 1 indicates that the underweight group was the smallest among all four BMI groups, with 6,759 individuals or 3.3% of the total study population. The overweight group was the largest with 67,687 individuals, or 33.0% of the study population.

When grouping all BMI categories together, the majority of individuals were white (55.5%) and male (60.4%). The largest percentage of study participants had private insurance (41.6%), followed by Medicare (36.5%). The largest number of participants received a high school of GED-level education (32.5). Only 4.9% received a graduate degree.

Following a general descriptive analysis of the study population, a survival analysis was performed. The probability of survival for each BMI group was examined through 15 years post-transplant.

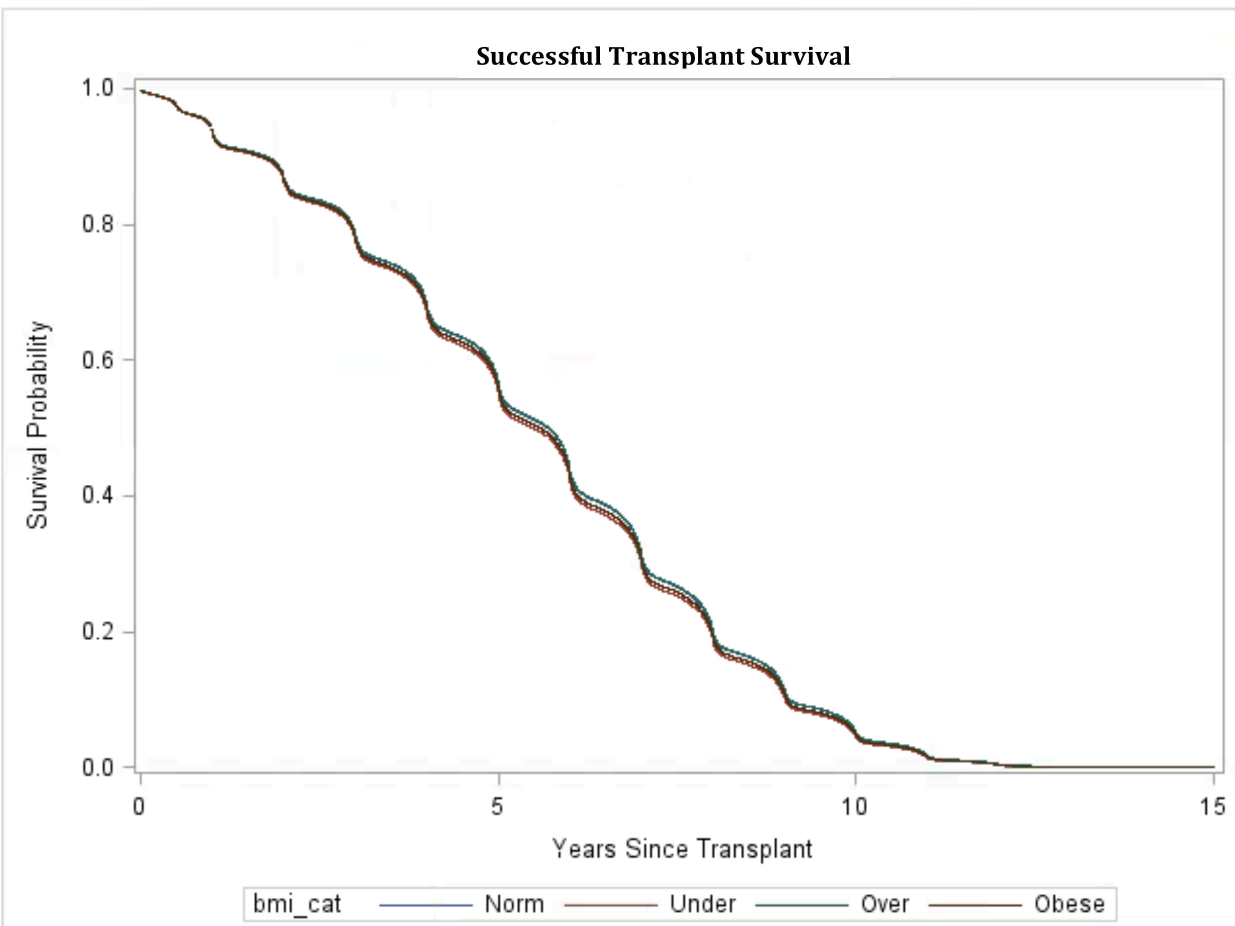

Figure 2. Survival Curve This survival curve represents the probability for survival in each BMI group for each year post-transplant, up to 15 years post-transplant.

Table 2. Confounding Variables The following table shows the p-value, hazard ratio and 95% confidence interval for the confounding variables of interest.

	Pr>ChiSq	Hazard Ratio	95% CI
BMI Category			
Normal	Reference		
Underweight	0.0074*	1.040	1.011, 1.071
Overweight	0.5527	0.997	0.985, 1.008
Obese	0.0002*	1.023	1.011, 1.036
Race/Ethnicity			
White	Reference		
Asian	0.0003*	0.960	0.939, 0.981
Black/African American	<0.0001*	1.098	1.085, 1.111
Hispanic/Latino	0.0317*	0.983	0.968, 0.999
Other/Unknown	0.1414	1.028	0.991, 1.067
Education			
Some College	Reference		
Less than HS	0.1362	0.981	0.957, 1.006
HS/GED	0.2401	0.992	0.980, 1.005
College Degree	<0.0001*	0.967	0.951, 0.983
Grad Degree	0.0250*	0.975	0.954, 0.997
None/Unknown	0.6836	1.003	0.988, 1.019
Gender			
Male	Reference		
Female	<0.0001*	0.948	0.939, 0.958
Insurance			
Private	Reference		
Medicaid	<0.0001*	1.089	1.067, 1.112
Medicare	<0.0001*	1.143	1.132,

			1.155
Other Government	0.0020*	0.966	0.930, 1.002
Other/Unknown	0.0020*	1.080	1.029, 1.134
Diabetes			
Has Diabetes	Reference		
No Diabetes	<0.0001*	0.954	0.940, 0.967
Unknown	<0.0001*	1.093	1.073, 1.113
Age at listing	<0.0001*	1.001	1.001, 1.002
Transplant Year	<0.0001*	1.314	1.312, 1.317

Table 3. Number of individuals in each BMI category that experienced graft failure or death each year post-transplant. The percent values are calculated based on the remaining sample size for each BMI category each year.

	Underweight (%)	**Normal (%)**	**Overweight (%)**	**Obese (%)**
Year 1	577 (8.5)	5,892 (7.8)	5,473 (8.1)	4,669 (8.4)
Year 2	315 (5.1)	3,325 (4.8)	2,828 (4.5)	2,417 (4.8)
Year 3	305 (5.2)	2,999 (4.5)	2,662 (4.5)	2,333 (4.8)
Year 4	312 (5.6)	2,959 (4.7)	2,530 (4.5)	2,149 (4.7)
Year 5	258 (4.9)	2,706 (4.5)	2,400 (4.4)	1,883 (4.3)
Year 6	238 (4.8)	2,418 (4.2)	1,974 (3.8)	1,612 (3.8)
Year 7	189 (4.0)	1,996 (3.6)	1,680 (3.4)	1,321 (3.3)
Year 8	165 (3.6)	1,764 (3.3)	1,464 (3.0)	1,051 (2.7)
Year 9	121 (2.8)	1,182 (2.3)	953 (2.0)	645 (1.7)
Year 10	80 (1.9)	922 (1.8)	780 (1.7)	489 (1.3)

Year 11	65 (1.5)	822 (1.7)	597 (1.3)	359 (1.0)
Year 12	48 (1.2)	608 (1.3)	423 (1.0)	254 (0.7)
Year 13	23 (0.6)	440 (1.0)	347 (0.8)	176 (0.5)
Year 14	44 (1.1)	337 (0.7)	214 (0.5)	116 (0.3)
Year 15	32 (0.8)	294 (0.6)	196 (0.5)	77 (0.2)

Analysis

The statistical analysis revealed numerous statistically significant ($p<0.05$) differences between the different BMI groups, confounding variables and long-term transplant success.

As anticipated by some of the current literature, Table 2 shows that, compared to individuals in the normal BMI category, obese individuals had a 2.3% ($p<0.005$) increase in hazard rate for graft failure over the study period. There was a 4.0% ($p<0.05$) increase in hazard rate for underweight individuals compared to individuals with a normal BMI. Overweight individuals did not have a statistically significant result. There was no statistically significant difference in the hazard rate for underweight individuals compared to those in the normal BMI category. Therefore, individuals who are underweight or obese are more likely to experience kidney transplant failure than individuals who are classified as having a normal BMI. Interestingly, individuals in the overweight BMI category at the time of kidney transplant did not show a statistically significant difference in long-term success compared to individuals in the normal BMI category. This finding supports the hypothesis that there would be no statistically significant difference between higher BMI groups and long-term transplant success.

Regarding race/ethnicity, Black and African American individuals had a 9.8% ($p<0.0001$) increase in hazard rate compared to White individuals, while Hispanic and Latino individuals had a 1.7% ($p<0.05$) decrease in hazard rate compared to Whites. Therefore, Black and African American individuals are more likely to experience kidney transplant failure within the first 15 years post-transplant than White individuals, while individuals who are Hispanic and Latino are less likely. Asian individuals also showed a decreased hazard rate (4.0%; $p<0.0005$) compared to White individuals, meaning that Asian individuals are also about 4% less likely to experience kidney transplant failure.

Compared to individuals who had some college experience, individuals with only a high school or GED-level education did not experience a statistically significant difference in hazard rate. However, compared to individuals with some college experience, individuals with a college degree and individuals with a graduate degree both experienced a decrease in hazard rate (3.3%, $p<0.0001$ and 2.5%, $p<0.05$ respectively). These individuals are less likely to experience a kidney transplant failure than individuals with only some college experience.

Compared to males, females had a 5.2% ($p<0.0001$) reduction in hazard rate. This means that on average, women are less likely to have kidney transplant failure than men. While statistically significant, the clinical significance of this result is likely limited. Therefore, gender should play a limited role in future transplant policy.

Patients on Medicare showed a 14.3% ($p<0.0001$) increase in hazard rate compared to individuals with private insurance. Individuals on Medicaid insurance also experienced an increased hazard rate (8.9%, $p<0.0001$) compared to individuals on private insurance. Therefore, individuals with Medicare or Medicaid are more likely than individuals with private insurance to experience a kidney transplant failure. Individuals on other government insurance experienced a 3.4% ($p<0.005$) decrease in hazard rate compared to individuals with private insurance and individuals with other or unknown insurance experience a statistically significant increase of hazard rate of 8.0% ($p<0.005$) compared to individuals with private insurance.
Compared to individuals with diabetes, individuals without diabetes had a 4.6% ($p<0.0001$) decrease in hazard rate and those with an unknown diabetes status saw a 9.3% ($p<0.0001$) increase in hazard rate.

According to the results in Table 2, for each additional year older an individual was at the time they were placed on the transplant list, they experienced a 0.1% ($p<0.0001$) decrease in hazard rate. This means that as age increases, the occurrence of kidney transplant failure decreases. This is contrary to the expected relationship between age and the dependent variable.

There was a 31.4% ($p<0.0001$) increase in hazard rate for each additional year past 2001 in which an individual's transplant occurred. This means that individuals who received a transplant more recently had an increased hazard rate compared to individuals who had a kidney transplant in the 90s.

Figure 2, a 15-year survival curve, shows that with each additional year post-transplant, there is a reduction in survival probability for all BMI groups. No BMI category appears to have a drastically different survival probability at any given time compared to the other BMI categories.

Table 3 provides the number of graft failures and deaths for each BMI category each year post-transplant. The percentages provided in the table are calculated by BMI category and are based on the remaining number of individuals in each category. The greatest percentage of graft failure or death in the first year post-transplant was seen in the underweight BMI category (577 individuals; 8.5%). However, this is not much greater than the percentages for the obese, overweight and normal BMI categories (8.4%, 8.1% and 7.8% respectively). The percent of individuals in each BMI group that experience a graft failure or die each year post-transplant continues to decrease the longer the follow-up time. This is to be expected, as the slope shown in Figure 2 is steeper at the beginning and nearly levels off toward the end of the 15-year follow-up period.

Chapter 5: Discussion

Introduction

The purpose of this study was to examine if different BMI categories are associated with differing long-term kidney transplant success. Current literature on this relationship is very diverse and inconclusive. By using a large, multi-year data set, this study is able to add to the current literature and influence future health policy.

Strengths and Limitations

This study had several strengths. The data set used for analysis was large (N=205,411). This resulted in a strengthened ability to detect small differences in outcomes. Furthermore, a long timespan was included in this study (1990-2013). This allowed for more individuals to be included in the analysis.

There were also several limitations to this study. There were several unmeasured patient characteristics related to both obesity and transplant outcomes. Omitting these characteristics could have resulted in inaccurate results. Additionally, the relationship between obesity and health is bi-directional. Thus, it must be acknowledged that individuals who are in very poor health may end up being very thin, while individuals who are very thin may end up having poor health.

Implications

Most transplant programs in the US currently have a BMI cut-off that prevents very obese individuals from being allowed on the transplant list.[76] The results from this study indicate that there is a statistically significant difference in the survival probability of individuals in the different BMI categories, specifically individuals who are underweight or obese. However, the clinical significance for individuals in either category is likely very limited. Therefore, transplant programs must review their protocols to ensure that individuals are not being excluded from kidney transplant programs only because of their BMI.

Individuals in the underweight BMI category saw a greater increase in hazard rate compared to normal BMI individuals than individuals in the obese category (4.0% vs. 2.3%). While the increases are small, the clinical implications are potentially greater for individuals in the underweight BMI category. Therefore, in order to promote efficient use of kidneys, a general policy should be made regarding underweight individuals receiving a kidney transplant. While they might not need to be excluded from the waitlist, it could be required that they enter a program that focuses on nutrition and healthy behaviors as a way to potentially increase their BMI before receiving the transplant. Similar programs could be required for obese individuals as well as a means of decreasing their BMI before transplant surgery. By creating one policy for all transplant programs, no single program will be called out for focusing on certain individuals. This will help create uniformity among transplant programs and will results in the greatest likelihood of increased survival for transplant patients.

Future Research

Future studies should be conducted using the most recent transplant recipient data to verify that BMI continues to have significant implications on kidney transplant success. Furthermore, studies need to identify and evaluate other potential factors that influence long-term success, including co-morbidities and lifestyle choices, like exercise and sleeping habits. Furthermore, research should examine the differences in outcomes based on primary insurance. These confounding variables showed a statistically and clinically significant difference, meaning that they may play a larger role in long-term transplant outcomes than previously considered. By identifying factors that contribute to differences in transplant success, changes to transplant policy can be made to increase success for all transplant recipients.

Conclusion

In conclusion, a BMI in the overweight category does not have a statistically significant impact on long-term transplant survival. However, a BMI in the underweight or obese categories does have a statistically significant, and potentially clinically significant, impact on long-term transplant survival. Therefore, transplant programs should review current protocols to ensure that individuals in the overweight category are not being prevented from receiving a transplant. Individuals in the underweight category should be provided with resources to encourage them to gain weight before receiving a kidney transplant, while individuals in the obese category should receive resources that encourage them to loose weight prior to surgery. Future policies should also be focused on additional variables, such as race/ethnicity and insurance type, since these variables showed both statistically and clinically significant differences.

References

1. Sifferlin, A. (2014, December 23). How the First Successful Kidney Transplant Happened. Retrieved from http://time.com/3644215/history-kidney-transplant/

2, 3. (2016). Retrieved September 3, 2016, from https://www.kidney.org/news/newsroom/factsheets/Organ-Donation-and-Transplantation-Stats

4. Transplant Trends. (n.d.). Retrieved from https://www.unos.org/data/transplant-trends/

5,18. Bentley, T. Scott. 2014 U.S. Organ and Tissue Transplant Cost Estimates and Discussion. Publication. Brookfield: Milliman, 2014.

6. "End Stage Renal Disease (ESRD) Symptoms, Treatments, & Causes - American Kidney Fund." End Stage Renal Disease (ESRD) Symptoms, Treatments, & Causes - American Kidney Fund. February 11, 2008. Accessed February 12, 2016. http://www.kidneyfund.org/kidney-disease/kidney-failure/end-stage-renal-disease/.

7,15. Bastani, Bahar. 2015. "The Worsening Transplant Organ Shortage in USA; Desperate Times Demand Innovative Solutions." *Journal of Nephropathology* 4 (4): 105–9. doi:10.12860/jnp.2015.20.

8. Narres, Maria, Heiner Claessen, Sigrid Droste, Tatjana Kvitkina, Michael Koch, Oliver Kuss, and Andrea Icks. 2016. "The Incidence of End-Stage Renal Disease in the Diabetic (Compared to the Non-Diabetic) Population: A

Systematic Review.” *Plos One* 11 (1): e0147329. doi:10.1371/journal.pone.0147329.

9. DiMaria, Christine, and Marijane Leonard. "End-Stage Kidney Disease." Healthline. November 24, 2015. Accessed February 12, 2016. http://www.healthline.com/health/end-stage-kidney-disease#Causes2.

10,11. National Kidney Foundation. (2007). A "New Normal": Life on Dialysis - The First 90 Days. Retrieved from https://www.kidney.org/sites/default/files/docs/11-10-0307_dialysistransitionbk2_oct07_lr_bm.pdf

12. "Transplant Trends." UNOS: United Network for Organ Sharing. Accessed January 28, 2016. https://www.unos.org/data/transplant trends/#waitlists_by_organ.

13. "Data." Organ Procurement and Transplantation Network, February 12, 2016. Accessed February 12, 2016. https://optn.transplant.hrsa.gov/converge/latestData/rptData.asp.

14. Klein, A. S., E. E. Messersmith, L. E. Ratner, R. Kochik, P. K. Baliga, and A. O. Ojo. "Organ Donation and Utilization in the United States, 1999-2008." American Journal of Transplantation 10, Part 2 (December 10, 2010): 973-86.

16. Diabetes Latest. (2014, June 17). Retrieved from http://www.cdc.gov/features/diabetesfactsheet/

17. Mandal, A. (2011, September 15). Demand for kidney transplant and dialysis increases due to diabetes prevalence. Retrieved from http://www.news-medical.net/news/20110915/Demand-for-kidney-transplant-and-dialysis-increases-due-to-diabetes-prevalence.aspx

19. Kidney Disease by the Numbers. (n.d.). Retrieved from http://mcdermott.house.gov/index.php?option=com_content&view=article&id=381&Itemid=62

20. Statistics. (n.d.). Retrieved from https://pharm.ucsf.edu/kidney/need/statistics

21. Immunosuppressants. (2015). Retrieved from https://www.kidney.org/atoz/content/immuno

22. Gordon, Elisa J., Thomas R. Prohaska, and Ashwini R. Sehgal. "The Financial Impact of Immunosuppressant Expenses on New Kidney Transplant Recipients." Clin Transplant 22 (2008): 738-48. Accessed February 13, 2016.

23. Coverage of immunosuppressant drugs and vitamins. (2017). Retrieved from https://www.medicareinteractive.org/get-answers/medicare-covered-services/medicare-and-end-stage-renal-disease-esrd/coverage-of-immunosuppressant-drugs-and-vitamins

24. Massey, E. K., Tielen, M., Laging, M., Beck, D. K., Khemai, R., Van Gelder, T., & Weimar, W. (2013). The role of cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: A cohort study. Journal of Psychosomatic Research, 75, 229-234.

25. Tushla, L. E. (n.d.). When A Transplant Fails. Retrieved from https://www.kidney.org/transplantation/transaction/TC/summer09/TCsm09_TransplantFails

26. About Adult BMI. (2015, May 15). Retrieved August 09, 2016, from https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

27. Sifferlin, A. (2013, August 26). Why BMI Isn't The Best Measure for Weight (or Health). TIME.

28. Lewis, T. (2013, August 22). BMI Not a Good Measure of Healthy Body Weight, Researchers Argue. Retrieved from http://www.livescience.com/39097-bmi-not-accurate-health-measure.html

29. Centers for Disease Control. (2015, May 15). Body Mass Index (BMI). Retrieved from https://www.cdc.gov/healthyweight/assessing/bmi/

30, 32. Park, J., Ahmadi, S. F., Streja, E., Molnar, M. Z., Flegal, K. M., Gillen, D., … Kalantar-Zadeh, K. (2014). Obesity paradox in end-stage kidney disease patients. *Progress in Cardiovascular Diseases*, *56*(4), 415–425. http://doi.org/10.1016/j.pcad.2013.10.005

31, 33. Khwaja, A., & El-Nahas, M. (2012). Transplantation in the obese: Separating myth from reality. *Nephrology Dialysis Transplantation*, *27*(10), 3732–3735. http://doi.org/10.1093/ndt/gfs406

34. Body Mass Index (BMI). (2014, August). Retrieved from https://www.betterhealth.vic.gov.au/health/healthyliving/body-mass-index-bmi

35, 39, 47. Aalten, J., Christiaans, M. H., de Fijter, H., Hené, R., van der Heijde, J. H., Roodnat, J., … Hoitsma, A. (2006). The influence of obesity on short- and long-term graft and patient survival after renal transplantation. *Transplant International : Official Journal of the European Society for Organ*

Transplantation, *19*(11), 901–907. http://doi.org/10.1111/j.1432-2277.2006.00367.x

36, 40. Grosso, G., Corona, D., Mistretta, A., Zerbo, D., Sinagra, N., Giaquinta, A., . . . Veroux, M. (2012, September). The role of obesity in kidney transplantation outcome. Transpant Proc, 44(7), 1864-1868.

47, 38, 41, 42. Johnson, D. W., Isbel, N. M., Brown, A. M., Kay, T. D., Franzen, K., Hawley, C. M., . . . Nicol, D. L. (2002, September 15). The effect of obesity on renal transplant outcomes. Transplantation, 74(5), 675-681.

43. Hill, C. J., Courtney, A. E., Cardwell, C. R., Maxwell, A. P., Lucarelli, G., Veroux, M., . . . McCaughan, J. A. (2015). Recipient obesity and outcomes after kidney transplantation: A systematic review and meta-analysis. Nephrol Dial Transplant, 0, 1-9.

44. Delayed Graft Function (DFG). (n.d.). Retrieved from

http://www.uwhealth.org/healthfacts/transplant/7103.pdf

45. Gore, J. L., Pham, P. T., Danovitch, G. M., Wilkinson, A. H., Rosenthal, J. T., Lipshutz, G. S., & Singer, J. S. (2006). Obesity and outcome following renal transplantation. *American Journal of Transplantation*, *6*(2), 357–363. http://doi.org/10.1111/j.1600-6143.2005.01198.x

46. Cannon, R. M., Jones, C. M., Hughes, M. G., Eng, M., & Marvin, M. R. (2013, May). The impact of recipient obesity on outcomes after renal transplantation. Ann Surg, 257(5), 978-984.

48. Pischon, T., & Sharma, A. M. (2001). Obesity as a risk factor in renal transplant patients. Nephrol Dial Transplant, 16, 14-17.

49. Curran, S. P., Famure, O., Li, Y., & Kim, S. J. (2014, January 15). Increased recipient body mass index is associated with acute rejection and other adverse outcomes after kidney transplantation. Transplantation, 97(1), 64-70.

50. Kieszek, R., Kwiatkowski, A., Jedrzejko, K., Domagala, P., Bieniasz, M., Wszola, M., . . . Chmura, A. (2014, October). Impact of pretransplant body mass index on early kidney graft function. Transplant Proc, 46(8), 2689-2691.

51. Tremblay, S., Kaiser, T. E., Alloway, R. R., Woodle, E. S., & Diwan, T. S. (2016, June). Absence of the Effect of Pretransplant Body Mass Index on Post Kidney Transplant Outcomes. Prog Transplant, 26(2), 183-190.

52, 54. University of Manitoba. Andersen and Newman Framework of Health Services Utilization. (n.d.). Retrieved from https://www.umanitoba.ca/faculties/health_sciences/medicine/units/chs/departmental_units/mchp/protocol/media/Andersen_and_Newman_Framework.pdf

53. Demand Theory. (2017). Retrieved from http://www.investopedia.com/terms/d/demand_theory.asp

55. Villareal, D. T., Apovian, C. M., Kushner, R. F., & Klein, S. (2005). Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. The American Journal of Clinical Nutrition, 82(5), 923-934. Retrieved from http://ajcn.nutrition.org/content/82/5/923.full

56. Nyberg, G., Blohme, I., & G. N. (1997). Gender differences in a kidney transplant population. Nephrol Dial Transplant, 12.

57, 60. "National Health and Nutrition Examination Survey." *CDC*. Centers for Disease Control, July 2003. Web. https://www.cdc.gov/nchs/data/nhanes/databriefs/adultweight.pdf.

58. Campbell, M. (2016, March 8). The Body Mass Index in Males vs. Females. Retrieved from http://www.livestrong.com/article/356517-the-body-mass-index-in-males-vs-females/

59. Nilakantan, V., Singh, M., Perez, R. M., Shi, Y., Dalmar, A., Last, B. T., & Sahajpal, A. (2016, January 25). Racial Disparities in Outcomes Following Kidney Transplantation: A Single-Center Experience. Journal of Patient-Centered Research and Reviews, 3(1), 9-19.

61. Prendergast, M. B., & Gaston, R. S. (2010). Optimizing Medication Adherence: An Ongoing Opportunity To Improve Outcomes After Kidney Transplantation. Clin J Am Soc Nephrol, 5, 1305-1311.

62. Goldfarb-Rumyantzev, A. S., Koford, J. K., Baird, B. C., Chelamcharla, M., Habib, A. N., Wang, B., . . . Isaacs, R. B. (2006, March). Role of Socioeconomic Status in Kidney Transplant Outcome. Clinical Journal of the American Society of Nephrology, 1(2), 313-322.
63. Schaeffner, E. S., Mehta, J., & Winkelmayer, W. C. (2008, May). Educational Level as a Determinant of Access to and Outcomes After Kidney Transplantation in the United States. American Journal of Kidney Diseases, 51(5), 811-818.
64. Adult Obesity Rates by Age and Education Level, 2008. (2008). Retrieved from https://trends.collegeboard.org/education-pays/figures-tables/adult-obesity-rates-age-and-education-level-2008
65. Mayo Clinic (2014, May 6). 5-year survival of diabetes and non-diabetes patients post-kidney transplant now nearly equal. Retrieved from https://www.sciencedaily.com/releases/2014/05/140506161236.htm
66. Bays, H. E., Chapman, R. H., Grandy, S., & SHIELD Investigators' Group. (2007). The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. International Journal of Clinical Practice, 61(5), 737-747. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1890993/.
67. Corbett, C., Armstrong, M. J., Parker, R., Webb, K., & Neuberger, J. M. (2013, October 15). Mental health disorders and solid-organ transplant recipients. Transplantation, 96(7), 593-600.
68. United for Sight. Urban Versus Rural Health. (2015). Retrieved from http://www.uniteforsight.org/global-health-university/urban-rural-health

69. Georgetown Health Policy Institute. Rule and Urban Health. (2003, January). Retrieved from https://hpi.georgetown.edu/agingsociety/pubhtml/rural/rural.htmlRule and Urban Health. (2003, January). Retrieved from https://hpi.georgetown.edu/agingsociety/pubhtml/rural/rural.html

70. About Adult BMI. (2015, May 15). Retrieved from https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

71. Mayo Clinic Staff. Diabetes. (2014, July 31). Retrieved from http://www.mayoclinic.org/diseases-conditions/diabetes/basics/risk-factors/con- 20033091

72, 73. SRTR -- Scientific Registry of Transplant Recipients. Retrieved March 25, 2016, from http://www.srtr.org/data_request/saf.aspx

74. Organ Procurement and Transplantation Network. Data Collection. March 9, 2016. Retrieved March 25, 2016, from https://optn.transplant.hrsa.gov/data/about-data/data-collection/

75. SRTR – Scientific Registry of Transplant Recipients. SAF Data Dictionary – 2016 Q1 External Release. Retrieved March 25, 2016, from http://www.srtr.org/data_request/content/datadictionary/current/default.html

76. National Kidney Foundation. Your Weight Before and After Kidney Transplant. (2016). Retrieved from https://www.kidney.org/content/your-weight-after-kidney-transplant