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Master of Public Health

Epidemiology

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Dr. Jessica Harding, PhD

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Bachelor of Science in Public Health

The Ohio State University

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Thesis Committee Chair: Dr. Jessica Harding, PhD

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A thesis submitted to the faculty of the

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Abstract

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By Margo Bowers

In 2021, over 800,000 individuals were living with end-stage kidney disease (ESKD) in the United States.[1] ESKD patients require treatment to survive, and despite clear benefits of transplant over dialysis for many people with ESKD, only 4% of patients on dialysis in 2021 received a transplant.[1] In this context of scarce organ supply, inequities in access to kidney transplantation exist. In particular, women with ESKD are ~20% less likely to be waitlisted for a kidney transplant,[1] and whether this disparity differs regionally in the US remains unknown. Identifying geographic 'hot spots' where sex inequities are greatest (and least) may shed light on potential mechanisms and allow for targeted interventions. In this retrospective cohort study, we identified adults (18-90) initiating kidney replacement therapy (KRT) between 2015-2019 from the United States Renal Disease System (USRDS). 'Sex' was ascertained from the Centers for Medicare & Medicaid Services Medical Evidence Form (CMS-2728), and geography was defined by the 18 End-Stage Renal Disease (ESRD) Networks managing ESKD patient care in the US. The primary outcome was time to waitlisting, measured as time between initiating KRT and being waitlisted. Cumulative incidence of waitlisting was estimated overall, by sex, and by ESRD Network with death as a competing risk. Cox-proportional hazard models assessed the association of sex and time to waitlisting by ESRD Network, with a partially adjusted model controlling for clinical factors and a fully adjusted model controlling for both clinical and non-clinical factors. The cumulative incidence of waitlisting for men and women at study end were 22.4% and 18.5%, respectively. Overall, women were 17% less likely to be waitlisted compared to men (Crude HR: 0.83 [95% CI: 0.82, 0.84]) and ranged from women being 10-22% less likely in Networks 16 (states of AK, ID, MT, OR) and 14 (Texas), respectively. This disparity ranged from 5-17% in partially adjusted models, and from 2-19% in the fully adjusted models. Though ubiquitously disadvantageous to women across the US, this sex disparity is not explained by clinical factors and is notably stronger in certain regions. Future research should investigate mechanisms in which place of residence contributes to this disparity.

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Literature Review

Overview

In 2021, more than 800,000 individuals were living with end-stage kidney disease (ESKD) in the United States.[1] ESKD patients require treatment with dialysis or transplant to survive, and despite clear benefits of transplant over dialysis for many people with ESKD,[2] only 4% of ESKD patients on dialysis in 2021 received a transplant largely due to the limited availability of organs.[1] It is in this context that inequities in access to kidney transplantation exist. In particular, women with ESKD are ~20% less likely to be waitlisted for a kidney transplant despite similar if not better post-transplant survival as compared with men,[1,3] though the exact mechanisms remain unknown. In this review, I will summarize the existing literature on the national burden of ESKD in the US, sex-based disparities in access to kidney transplantation, and the potential contribution of where a person lives in understanding sex disparities in access to kidney transplant.

Epidemiology of End-Stage Kidney Disease (ESKD)

In 2021, more than 800,000 individuals were living with ESKD in the United States.[1] This number is expected to rise in the future largely due to an aging population, increased survival among ESKD patients owing to better treatments, and an increase in prevalent risk factors for ESKD among the general population such as diabetes and obesity.[1] ESKD is also very costly. Individuals with ESKD comprise just one percent of all Medicare beneficiaries, yet constitute seven percent of all Medicare spending.[4] These high spending costs can largely be attributed to ESKD patients needing expensive kidney replacement therapy (KRT) such as dialysis or transplantation to survive.[4]

The leading causes of ESKD are diabetes and hypertension, followed by autoimmune disorders, glomerulonephritis, and other inherited diseases such as polycystic kidney disease.[5] Other risk factors for ESKD include older age, obesity, family history of kidney disease, high blood pressure, Black race, and lower education attainment.[6] Following ESKD onset, typically indicated by the need to initiate KRT, the five-year survival probability of a patient varies by treatment modality.[1] The United States Renal Data System (USRDS) reported the five-year survival probability of individuals with a 2017 ESKD onset was 39.6% and 41.3% for patients on hemodialysis and peritoneal dialysis, respectively,[1] compared to 80.5% and 87.0% for patients who received a deceased or living donor kidney transplant, respectively.[1]

Treatment Options for ESKD

In 2021, 83.8% of all incident ESKD patients began in-center hemodialysis in the United States, followed with 12.7% and 0.4% beginning peritoneal dialysis (dialysis at home) or at home hemodialysis, respectively.[1] A kidney transplantation is considered the optimal treatment for the majority of ESKD patients as it is associated with lower mortality, reduced risk of future cardiovascular events, and improved quality of life as compared with dialysis.[2] Transplant is also cheaper than dialysis – In 2021, Medicare spent over $99,000 per individual on hemodialysis, ~$87,000 per individual on peritoneal dialysis, and just ~$44,000 per transplant.[1]

Unfortunately, the process of receiving a kidney transplant is complex and involves engagement from patients across multiple health systems, **Figure 1**.[7] Though requirements vary by center, the process of a kidney transplant generally begins with educating ESKD patients about transplantation typically in a dialysis facility or with a nephrologist. Individuals are then referred from a nephrologist or primary care practitioner to initiate the transplant evaluation process at a transplant center. The evaluation process consists of education-based training and various medical examinations by the transplant team to determine transplant eligibility. Once transplant evaluation has been completed and approved, the patient is placed on a national deceased donor waiting list until a living or deceased donor kidney is made available to them for transplantation.[7]

Figure 1. Steps in Receiving a Kidney Transplantation

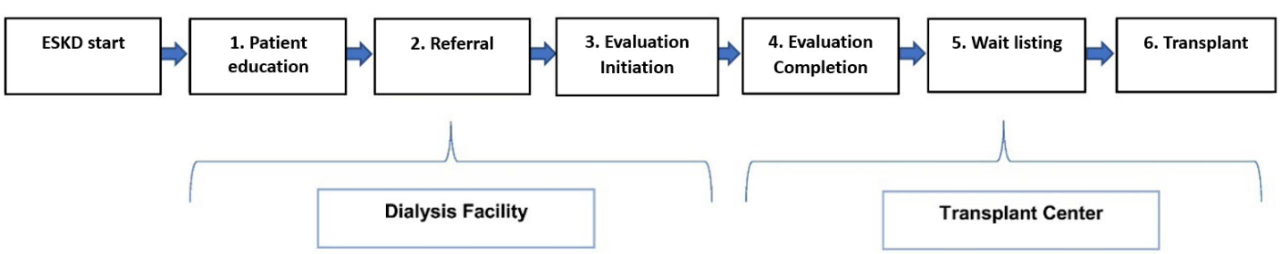


Figure edited from Harding et al. (2021) Transplant Rev (Orlando). 2021;35(4):100654. Doi: 10.1016/j.trre.2021.100654

Disparities in Access to Kidney Transplantation

Limited availability of organs, coinciding with the rising number of people living with ESKD, contributes to inequities in access to kidney transplantation. The reasons for disparities in access to transplant among these groups are likely multifactorial and operate at various levels, including the patient-, provider-, and system-levels. A large body of evidence documents that several groups have reduced access to transplant compared to others including Hispanic,[8] Pacific Islander,[9] Black,[10–12] and Indigenous Americans,[8] individuals with public health insurance,[13–15] and older patients.[8,14,16] Additional patient-level barriers to transplant access include lack of transplant knowledge,[17] patient perceived inaccessibility to ESKD-trained staff,[17] low socioeconomic status,[18] lack of transportation,[18] societal or cultural values,[13] and lack of social support.[13] At the provider-level, identified barriers include inadequate communication between patients and providers,[13,17,18] provider perceived lack of patient interest or ineligibility for transplant,[19] and limited availability of experienced staff.[20] At the neighborhood- or systems-level, neighborhood poverty,[14,18] distance to care,[12] dialysis facility for-profit status,[14] institutional-level healthcare logistics,[13] and geography,[11,20–23] have all been linked to reduced access at various stages of the transplant process.

Sex-Based Disparities in Access to Kidney Transplantation

Women (vs. men) have reduced access to multiple transplant steps across the transplant care continuum, including prior to KRT initiation.[24] Specifically, men were twice as likely to undergo KRT compared to women across various European countries,[25] despite having lower prevalence of chronic kidney disease (CKD).[1] A study from Sweden investigated other indices of CKD care and found that compared to men, women were half as likely to visit with a nephrologist or to receive a diagnosis for CKD, and ~30% less likely to receive guideline-recommended CKD treatments such as statins or reninangiotensin inhibitors.[26] Sex disparities also persist further downstream on the transplant care continuum.[24] Evidence, primarily from the Southeast US, demonstrates that women are less likely to be referred or evaluated for a kidney transplant.[27] Specifically, women are ~10% less likely to be referred and ~7% less likely to be evaluated when compared to men in the Southeastern US.[27] The same study found that if women made it through the necessary transplant steps of referral and evaluation, they then had a comparable likelihood of being waitlisted or transplanted to men, suggesting that earlier vs later transplant steps may be more important in driving the overall disparity in waitlisting seen nationally.[27] Furthermore, a large sex-based disparity can be seen in living donor transplants where women constitute 60% of all living donors in 2022, but only comprised 40% of those who received a living donor transplant.[1] Among ESKD patients undergoing dialysis, women accounted for less than 40% of living donor recipients in 2021.[1] Yet, over 60% of all living donors in 2022 were women.[3]

Though the true causes of these sex disparities remain unknown, it is likely a complex interplay of biological, social, and cultural factors, **Figure 2** contributes.[24] One biological sex factor is the quicker decline in the estimated glomerular filtration rate (eGFR) and faster progression of CKD among men.[28] This could create a perceived urgency among providers to prioritize kidney care for men compared to women. Pregnancy-induced sensitization is a biological sex factor that occurs with the presence of antihuman leukocyte antigen-antibodies that are sustained during pregnancy.[24] The presence of these antigen-antibodies can reduce histocompatibility during and after pregnancy, making it more difficult for women to find a suitable kidney donor match, but should not be a factor in women's likelihood of being waitlisted for transplant in the first place.[24] Further, active autoimmune disorders and less suitable panel-reactive antibody (PRA) statuses that impact patient transplant eligibility are more prevalent among women.[29]

Figure 2. Multi-Level Factors Contributing to Access to Kidney Transplant

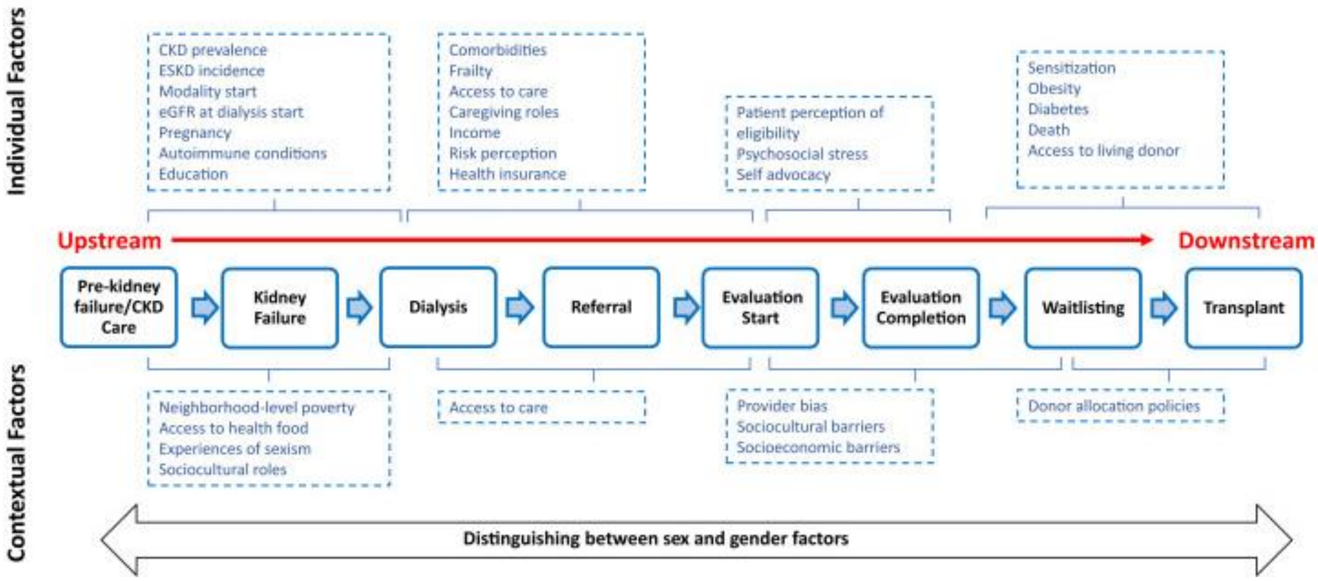


Figure taken from Harding JL. Women's Access to Kidney Transplantation. Kidney International Reports. 2024; 9(3):512-515. Published 2024 Jan 26. https://doi.org/10.1016/j.ekir.2024.01.040

Social factors span multiple levels (i.e., patient, provider, or neighborhood-level) and are influenced by sexism and discrimination. Obesity is more common among women, however, obese women have reduced access to transplant relative to equally obese men, suggesting a potentially larger influence from social factors and perceptions of obesity rather than biological differences.[30] Women often face obstacles in accessing medical care and are more likely to be delayed in initiating dialysis.[31] Furthermore, a transition from CKD to dialysis care that is unplanned compared to an optimal/suboptimal transition to dialysis initiation has been shown to increase risk of hospitalization or mortality.[32] Women more frequently self-rate their health as poor compared to men,[33] and have more personal concerns regarding asking for a living kidney donation or risks of receiving a transplant.[34] A 2014 study found that among ~350 ESKD patients initiating dialysis, women were 18% more likely (compared to men) to report concerns of fearing the transplant surgery and 11% more likely to perceive themselves as too weak to have a transplant.[34] This poorer self-rated health may in turn may influence provider-level biases deeming women less eligible for transplant as compared with men despite similar objective comorbidities and frailty levles.[15] Importantly, frailty can be modifiable.

Providers also seem less likely to discuss transplant as a treatment option among women with ESKD. A 2014 study in Maryland found that among 416 ESKD patients undergoing dialysis, women were 45% less likely to reporting having had discussions regarding kidney transplant as a potential treatment option as compared with men.[35] Though patient and provider-level factors likely explain a large portion of the observed sex disparity in access to kidney transplant, they do not provide the full context for why women have reduced access as compared with men. Recently, there has been a shift to looking beyond individual-level and provider-level factors and examining the impact of the broader contextual factors that may impact access to kidney transplant.

Geographic Variation in Health Outcomes

Where an individual resides has been shown to be associated with several health outcomes. Obesity, a common comorbidity among ESKD patients, is highly variable at the US county-level among the general population.[36] The county-level prevalence of obesity ranges from 14% to 48%, with high obesity prevalence clustering in Southern and Appalachian regions and low obesity prevalence clustering in the Western and Northeastern US.[36] In this context, it is no surprise that the Southern US also has a high prevalence of diabetes diagnoses.[37] States identified with the highest rates of diabetes were mainly in the South (OK, LA, AK, MS, AL, TN, SC, KY, WV), and the lowest rates were in the West (CO, UT, HI).[37] Mechanisms for variable health outcomes by geography are likely similar across chronic conditions such as obesity, diabetes, and kidney disease. Communities with high levels of structural vulnerabilities (e.g., proportion of Black households, proportion of households with multiple individuals over 65 years old)[38] and with poor socioeconomic composition (e.g., proportion of households receiving Supplemental Nutrition Assistance Program (SNAP) benefits to assist with food security and income inequality)[38] have previously been shown to have higher rates of cardiometabolic disease compared to higher socioeconomic status (SES) communities.[38] Another US study found that areas that remained predominantly Hispanic or predominantly non-Hispanic Black populations for over a decade had a higher risk of losing or never having healthcare facilities nearby compared to areas of predominantly non-Hispanic White populations.[39] These structural and neighborhood-level vulnerabilities are often a proxy for experiences of disadvantage and inequality and are not health-specific in nature.[38] However, they can serve as an upstream stressor that influences the distribution or access to resources, interpersonal relationships, and experiences of material hardship, all of which can induce poor health outcomes in these vulnerable communities.[38]

Geographical Variations in ESKD

Previous research has identified geographic variation in ESKD incidence, mortality, and transplant access that broadly align with patterns observed for other chronic conditions such as obesity, diabetes, and cardiometabolic diseases as discussed above. For example, in one 2020-2021 study defining geography using Health Service Areas (geographically defined areas where healthcare services are organized and received by community members), the ESKD incidence ranged from 195.6 to 907.4 per million people across the US, **Figure 3.**[1] Highest estimates were seen in Central California and Southern Texas, and lowest in New England, the Pacific Northwest, and the Rocky Mountain states (CO, AZ, NV, NM, WY, UT, ID, MT).[1]

Figure 3. Incidence of ESKD by Health Service Area, 2020-2021

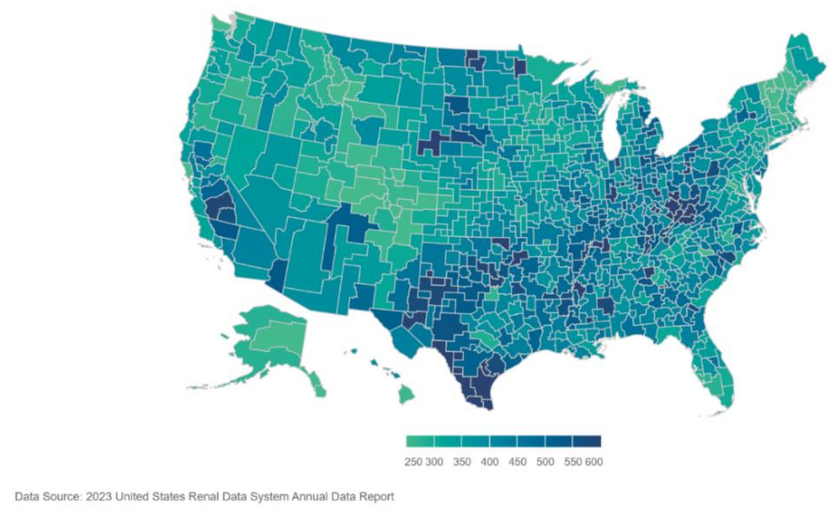


Figure taken from United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.

ESKD mortality also varies by geography. In a national study of county-level characteristics and ESKD mortality, Snow et al reported that age-adjusted ESKD mortality ranged from 45 to 1,022 per 1,000 person-years across US counties, with the highest estimates of ESKD mortality being among Appalachia and Tennessee Valley regions, and the lowest in New England, Southern California, and Pacific Northwest counties.[40] Interestingly, just 19% of this variation could be attributable to county-level characteristics including demographic, healthcare, socioeconomic, or heath behavior-related characteristics.[40] The remaining 81% remained unexplained.[40] These results mirror the findings among ESKD incidence.

Geographic variation in access to kidney transplant has also been shown. A study by King et al found local variation in the probability of receiving a deceased donor kidney transplant across Organ Procurement and Transplantation Network (OPTN) regions.[21] Variability between transplant centers was the highest in OPTN Region 4 (Texas and Oklahoma) with the probability of transplantation in 2015 ranging from 4.4% to 63.9%,[21] while OPTN Region 1 (New England) had the smallest variation ranging from 6.1% to 20.4%.[21] There are several mechanisms for which this variation may exist, including differences in eligibility criteria in accepting kidney donations across centers contributing to deceased donor kidney waste, and the historical geographic boundaries set in place for the allocation of kidney supply.[21] At the state-level, the rate of waitlisting among all ESKD patients ranged from being 37% lower to 64% higher relative to the national average between 1996 and 2005, as seen below, **Figure 4**. This variability has been attributed to attitudes and social norms towards treating illnesses, specifically ESKD or transplantation, among patient populations local to each individual state.[22]

Figure 4. Rate of waitlisting in ESKD patients by state, relative to the national average between 1996 and 2005

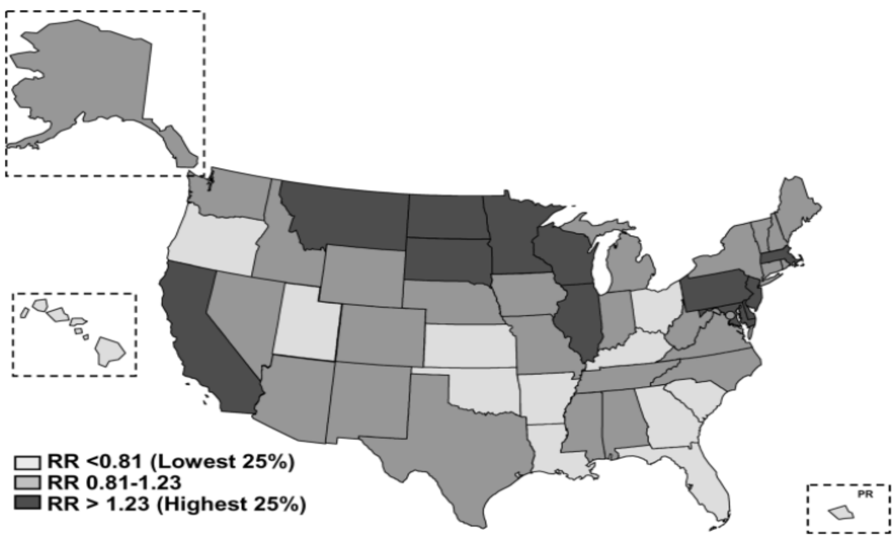


Figure taken from Ashby et al (2007). Ashby VB, Kalbfleisch JD, Wolfe RA, Lin MJ, Port FK, Leichtman AB. Geographic variability in access to primary kidney transplantation in the United States, 1996-2005. Am J Transplant. 2007.

In 2014, OPTN created a new Kidney Allocation System (KAS) to improve access to deceased donor kidney transplants and reduce geographical variation in allocation of kidneys at a regional and national level.[23] However, a 2018 study showed that deceased donor kidney transplant (DDKT) rates remained variable across organ allocation regions, or donation service areas (DSAs), before and after the implementation of KAS, suggesting that the new allocation system did not improve geographic disparities to transplant access as was intended.[23] However, the authors explain that a limitation to studying DSA-level geographic variation is the potential mediating effect of transplant center-level factors.[23] Patzer et al describes dialysis or center-level specific provider perceptions and behaviors, such as willingness to waitlist individuals with comorbidities, sense of urgency to waitlist, or differences in transplant center selection criteria as potential mechanisms exacerbating geographic variation in transplant access.[41]

A 2023 study by McPherson et al found that racial disparities in waitlisting rates varied by geographic regions.[11] Specifically, End-Stage Renal Disease (ESRD) Networks 11 (MI, MN, ND, SD, WI), 15 (AZ, CO, NM, NV, UT, WY), 10 (IL), and 18 (Southern CA) had the largest racial disparities, with Black individuals with ESKD being respectively 14%, 15%, 16%, and 29% less likely to be waitlisted compared to White individuals with ESKD.[11] Regions with the largest racial disparities tended to be areas with a smaller proportion of Black residents with ESKD.[11] The authors suggests that while there may be progress in reducing racial disparities in waitlisting in geographical regions with higher proportions of Black ESKD individuals, future interventions are needed to reduce inequities in regions with lower proportion of Black ESKD individuals.[11]

Geographical variation of sex disparities in transplant access

To date, there are no studies that have examined the intersection between sex and geography with respect to transplant access. However, research conducted for other chronic health outcomes supports the rationale that sex disparities in transplant access are likely to be conditional upon where a person lives. For example, a 2022 study by Carlson et al examined sex disparities in the age-adjusted mortality rate by determining the number of deaths attributable to chronic obstructive pulmonary disease (COPD) between 1999 and 2019 by US state.[42] Results found that, overall, mortality rates declined significantly among men in this time frame, yet for women with COPD, mortality changes were more state dependent.[42] For example, mortality rates decreased for women in 17 states, and these states were more likely to be in the West or Northeast.[42] Mortality rates for women increased in 18 states, and these states were mainly were in the South or the Midwest.[42] The authors first postulate that the sex disparity in age-adjusted COPD mortality rates could be related to biologic factors leaving women more susceptible to tobacco or smoking adverse effects, sex-specific disease presentations leading to delayed diagnosis among women, the delayed decline in cigarette smoking among women versus men, and systemic challenges faced by women in the healthcare system.[42] The study also notes an increase in the urban-rural disparity over the past 20 years,[42] a geographic change that could impact the burden of sex disparities. Specifically, adults living in rural areas likely have increased challenges in healthcare access and are more likely to be uninsured,[42] two socioeconomic factors that also tend to disproportionately impact women. Given the complex care needs of patients with ESKD, and the multiple systems patients must navigate to be waitlisted for a lifesaving transplant, all of which are impacted by local policies, cultures, and social factors, it is reasonable to hypothesize that geography may play an important role in understanding sex-based disparities in transplant access.

Figure 5. Change in Age-Adjusted COPD Mortality Rates, By State and By Sex (1999 - 2019)

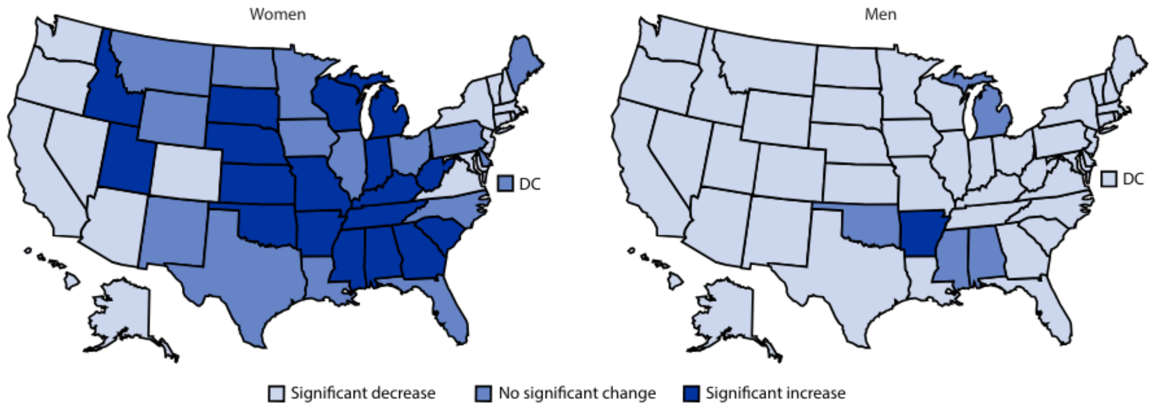


Figure taken from Carlson SA, Wheaton AG, Watson KB, Liu Y, Croft JB, Greenlund KJ. Geographic Differences in Sex-Specific Chronic Obstructive Pulmonary Disease Mortality Rate Trends Among Adults Aged ≥25 Years — United States, 1999–2019. MMWR Morb Mortal Wkly Rep. 2022;71(18):613-618. doi:10.15585/mmwr.mm7118a1

Conclusion

Kidney transplant is the optimal treatment for ESKD, but access remains inequitable for women. These disparities likely arise due to a complex interplay between several multi-level and multi-factorial mechanisms operating at the patient-, provider- and systems level. A growing body of research indicates that where a person lives is an important predictor of several health outcomes, yet it is unclear what role geography plays in sex-based disparities in transplant access in the US. Identifying geographic 'hot-spots' where sex-based disparities are greatest may help inform the development of targeted interventions to improve transplant access for women with ESKD where it is most needed.

Introduction

In the United States, more than 800,000 adults in 2021 were living with ESKD, which requires treatment with dialysis or transplant to survive.[1] On average, life expectancy among dialysis patients is between 5-10 years, but is considerably longer if a patient can receive a transplant, with a 10-15 year and 15-20 year life expectancy following a deceased or living donor kidney transplant, respectively.[5] In addition to improved life expectancy, transplantation offers better quality of life,[2] and is more cost effective as compared with dialysis.[1,4]

Unfortunately, despite the clear benefits of transplant for the majority of ESKD patients, only 4% of ESKD patients on dialysis in 2021 received a transplant largely due to the limited availability of organs.[1] In this setting, disparities in access to kidney transplants exist. For example, a wealth of evidence now documents that people of Black or Hispanic race, older adults, and people of low socioeconomic status (SES) have reduced access to transplant as compared with people of White race, younger age, and higher SES, respectively.[6] It has also been documented that women are ~20% less likely to be waitlisted or transplanted as compared with men,[1] though the exact mechanisms driving this disparity are unknown.

A growing body of evidence highlights the importance of where an individual lives for overall health, and healthcare access.[36–39] For example, people living in neighborhoods with high rates of income inequality, large proportion of Black residents, or residents receiving public assistance such as Supplemental Nutrition Assistance Program (SNAP) benefits to improve their food security, are all at increased risks for poor health outcomes such as decreased access to healthcare facilities and resources.[38] In the context of transplant, McPherson et al found that regions with the strongest racial disparities between Black and

White ESKD patients in transplant access tended to be areas with a smaller proportion of Black residents with ESKD.[11] It is possible, therefore, that geography may also interact with sex to impact transplant access for women with ESKD, yet this has not been explored before.

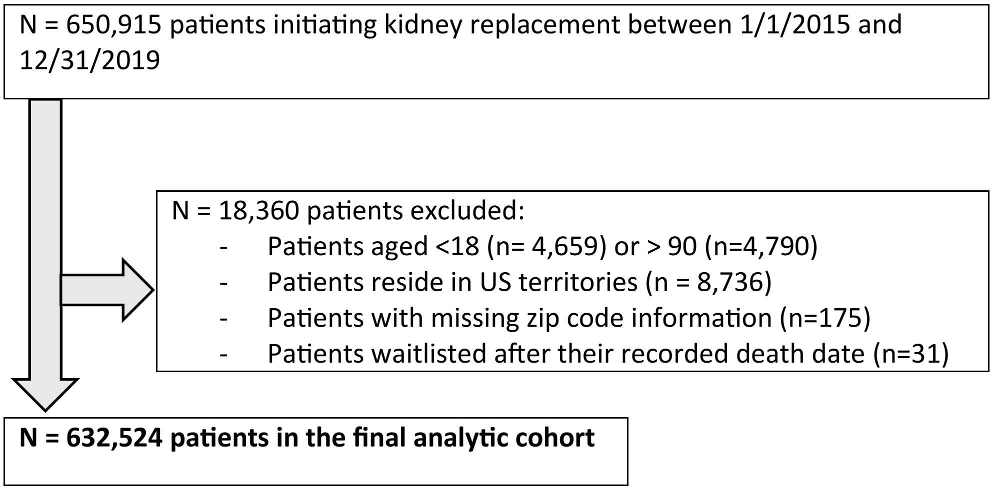
Therefore, in this study, we will examine geographic variation in sex-based inequities in access to the kidney transplant waitlist in the United States.

Methods

Study Population and Data Sources

This was a retrospective cohort study using data from the United States Renal Disease System (USRDS), a nationwide registry of all individuals initiating kidney replacement therapy (KRT; dialysis or transplantation) in the US. We included all adults (aged 18-90 years) initiating KRT between January 1, 2015, and December 31, 2019 (n= 641,466), with follow-up through December 31st, 2021 to ensure all individuals had a minimum of 2-years follow-up. Individuals were excluded if they did not reside in the United States (n= 8,736), did not have zip code information (n= 175), or had a waitlisting date recorded after a death date (n=31). The final cohort was composed of 632,524 individuals initiating KRT between 2015-2019, **Figure 6**.

Figure 6. Study cohort



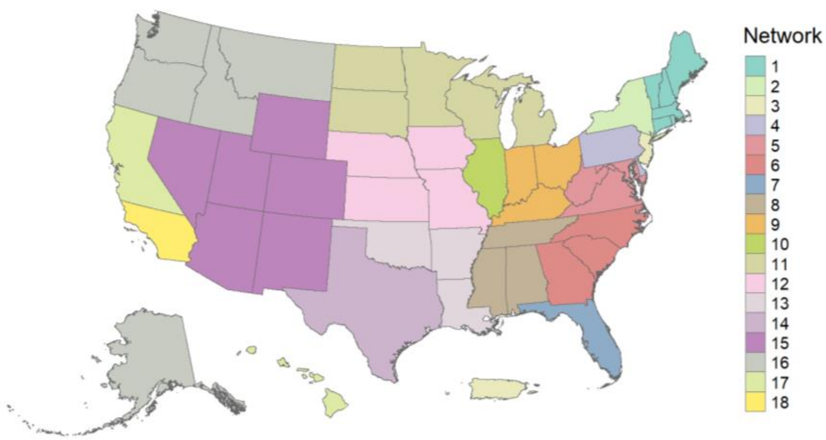
Sex Definition

Sex and gender are distinct terms that are often, incorrectly, used interchangeably. “Sex” refers to biological characteristics typically assigned at birth based upon genetics or sexual reproduction categorizations,[43] while “gender” describes roles, identities, and/or social norms experienced at an individual- and societal-level.[27] In this study, we will use ‘sex’ as captured on the Centers for Medicare & Medicaid Services Medical Evidence Form (CMS-2728), however, we acknowledge the role of both sex and gender in impacting transplant access, and though we use sex terminology throughout, our interpretation will include the complex interplay between both sex and gender. Further, due to the absence of nonbinary gender options on the CMS-2728 form for this study period, patients are categorized as “male” or “female” based on their healthcare provider’s perception of the patient’s sex when initiating KRT services. With this context, patients herein are assigned as “women” and “men”.

Geography

We defined geographical regions as ESRD Networks. ESRD Networks are defined by CMS as all the Medicare-approved ESKD facilities grouped within a geographic area.[44] Networks serve as their region's coordinating body to promote access to healthcare resources and improve patient care for individuals with ESKD.[44] The USRDS data assigns each patient's residential zip code to their designated ESRD Network. There are 18 ESRD Networks that cover the 50 US states, **Figure 7**.

Figure 7. End-Stage Renal Disease (ESRD) Network Map



Adapted from the ESRD National Coordinating Center. Accessed April 9, 2024. https://esrdncc.org/en/ESRD-network-map/ [45]

Access to Transplant

The primary outcome in this study was waitlisting, defined as the date a patient was added to the waitlist. For people with multiple listing dates, we took the first date only. Individuals were followed form date of KRT initiation, until waiting listing date, date of death, or end of follow-up (December 31, 2021), whichever occurred first. For patients whose first waitlisted date preceded their first date of receiving

KRT or where their first KRT was a transplant (i.e. pre-emptively waitlisted and transplanted patients, respectively), we defined follow-up time as one day.

Covariates

Participant demographic and clinical information was collected at KRT initiation using the CMS-2728 form, and included age (as a continuous variable in groups 18-39, 40-59, 60-74, 75-79, 80-84, and 85-90 years), attributed cause of ESKD (diabetes, hypertension, glomerulonephritis, cystic kidney disease, and other), and presence of comorbidities (obesity, congestive heart failure, atherosclerosis heart disease, cerebrovascular disease, peripheral vascular disease, other cardiac disease, hypertension, diabetes, COPD, cancer, tobacco use, and alcohol dependence). Obesity was categorized using patients' measured body mass index (BMI), with patients with a BMI > 35 kg/m^2 being classified as "obese". Other patient-level key variables from USRDS data included race and ethnicity (defined as non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic 'other' race which includes individuals identifying as Asian, American Indian or Alaskan Native, and Native Hawaiian or Pacific Islander), patient informed of transplantation being a treatment option (yes/no), pre-ESKD nephrology care (yes/no), patient dialysis modality (hemodialysis/peritoneal dialysis), and medical insurance coverage. Insurance coverage was hierarchically formatted to account for patients with more than one insurance provider, and were categorized in the following order: employer, Medicaid, Medicare, other, or none.

Neighborhood-level factors were determined from patient zip code and linked to the 2017-2021 American Community Survey (ACS) data. They include rural or urban area, neighborhood poverty level (categorized as high poverty if ≥ 20% of residents were living in poverty), average percentage of the population with a high school equivalent education or greater, average percentage of females in the total population, and the average percentage of Black individuals in the total population. All variables had less than 5% of data missing, except for pre-ESKD nephrology care (16.3% of individuals were missing data for this variable).

Statistical Analysis

Differences in baseline characteristics between men and women and across ESRD networks was described by frequencies and proportions (n, %), mean and standard deviation (SD) for normally distributed variables, and median and interquartile range (IQR) for non-normal variables, as appropriate. We similarly compared baseline characteristics among the overall study population, patients who were waitlisted, and patients who died prior to waitlisting, by ESRD network.

We estimated the cumulative incidence of waitlisting in men and women overall, by sex, and within each ESRD Network with death treated as a competing risk. The median follow-up time was also calculated overall, by sex, and by ESRD network. We then used Cox proportional hazard (PH) models, censored for death, to examine the association between sex and waitlisting overall and stratified by ESRD network. Similar to other work,[26] we believe that sex cannot be causally influenced by other factors (i.e., obesity cannot influence someone's sex) and thus there are no true confounders for the association between sex and waitlisting.[26] For this reason, we report our primary results as those from crude models, and utilize the interpretation of multivariable models to examine potential mediators on the pathway between sex and waitlisting. Multivariable adjustment was conducted in a two-step process. In a partially adjusted Cox PH model, we first adjusted for patient-level clinical factors such as age, attributed cause of kidney failure, and comorbidities. In our fully adjusted model, we additionally adjusted for non-clinical factors including race and ethnicity, primary health insurance status, patient being informed of transplant as a treatment option, pre-ESKD nephrology care, dialysis modality, rural or urban categorization of patients' residential zip code, and neighborhood level characteristics (poverty level, average percentage of females in the total population, average percentage of Black individuals in the total population, and average percentage of individuals who attained a high school education or higher). The Cox proportional hazards assumption was tested visually using Kaplan-Meier curves for the primary exposure of sex and did not indicate any violations. Multicollinearity was assessed using variance decomposition proportion for all covariates in the partially- and fully adjusted models. No covariates were removed following the multicollinearity assessment. Finally, to visualize the geographical variation of sex disparities in access to waitlisting between men and women, a map presenting the crude hazard ratio of waitlisting in women vs. men across the 18 ESRD Networks was made in R Studio. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina) and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). This study was approved by Emory University's Institutional Review Board (#IRB00063645).

Results

Baseline characteristics

Among 632,524 US adult ESKD patients initiating KRT between January 2015 and December 2019, 58% were men and 42% were women, **Table 1**. Compared to men, women were slightly younger, more likely to identify as non-Hispanic Black, have diabetes as an attributable cause of ESKD, have comorbid diabetes and obesity, have Medicaid as their primary health insurance, and live in neighborhoods with a higher percentage of Black residents or high poverty levels, **Table 1**. Women were also less likely than men to have most other comorbid conditions including atherosclerotic heart disease, peripheral vascular disease, other cardiac diseases, report tobacco use, and alcohol dependence, **Table 1**.

All 18 ESRD Networks had a higher percentage of men initiating KRT than women, **Table 2**. The largest difference was in Network 1 (New England) with 61% of patients being men and 39% being women. The smallest difference was in Network 13 (AR, LA, OK) with 55% men and 45% women, **Table 2.**

Table 1. Baseline Characteristics of ESKD patients who initiated KRT between 1/1/2015 and 12/31/2019, overall and by sex

ESKD Patient Characteristics	**Overall**	**Women**	**Men**
N (%)	632,524	265,223 (41.9%)	367,301 (58.1%)
Individual-level characteristics			
ESRD Network, n (%)			
1 (CT, MA, ME, NH, RH, VT)	20,070 (3.2)	7,895 (3.0)	12,175 (3.3)
2 (NY)	38,860 (6.1)	15,572 (5.9)	23,288 (6.3)
3 (NJ)	18,857 (3.0)	7,541 (2.8)	11,316 (3.1)
4 (DE, PA)	26,436 (4.2)	10,820 (4.1)	15,616 (4.3)
5 (DC, MD, VA, WV)	35,561 (5.6)	15,277 (5.8)	20,284 (5.5)
6 (GA, NC, SC)	56,500 (8.9)	25,078 (9.5)	31,422 (8.6)
7 (FL)	43,582 (6.9)	17,414 (6.6)	26,168 (7.1)
8 (AL, MS, TN)	34,564 (5.5)	15,516 (5.9)	19,048 (5.2)
9 (IN, KY, OH)	46,122 (7.3)	19,720 (7.4)	26,402 (7.2)
10 (IL)	26,856 (4.3)	11,366 (4.3)	15,490 (4.2)
11 (MI, MN, ND, SD, WI)	38,108 (6.0)	16,005 (6.0)	22,103 (6.0)
12 (IA, KS, MO, NE)	23,386 (3.7)	9,860 (3.7)	13,526 (3.7)
13 (AR, LA, OK)	26,226 (4.2)	11,790 (4.5)	14,436 (3.9)
14 (TX)	61,420 (9.7)	26,473 (10.0)	34,947 (9.5)
15 (AZ, CO, NM, NV, UT, WY)	32,652 (5.2)	12,979 (4.9)	19,673 (5.4)
16 (AK, ID, MT, OR, WA)	19,628 (3.1)	7,931 (3.0)	11,697 (3.2)
17 (Northern CA, HI)	31,832 (5.0)	12,937 (4.9)	18,895 (5.1)
18 (Southern CA)	51,864 (8.2)	21,049 (7.9)	30,815 (8.4)
Age (years)			
Median (IQR)	64 (54-73)	65 (55-74)	64 (53-73)
18 – 39	48,606 (7.7)	20,878 (7.9)	27,728 (7.6)
40 – 59	188,134 (29.7)	72,674 (27.4)	115,460 (31.4)
60 – 74	253,778 (40.1)	109,825 (41.4)	143,953 (39.2)
75 – 79	67,114 (10.6)	29,536 (11.1)	37,578 (10.2)
80 - 84	47,873 (7.6)	20,720 (7.8)	27,153 (7.4)
85 - 90	27,019 (4.3)	11,590 (4.4)	15,429 (4.2)
Race			
Non-Hispanic White	333,615 (52.7)	133,551 (50.4)	200,064 (54.5)
Non-Hispanic Black	161,107 (25.5)	74,916 (28.3)	86,191 (23.5)
Hispanic	93,541 (14.8)	37,928 (14.3)	55,613 (15.1)
Other	41,575 (6.6)	17,765 (6.7)	23,810 (6.5)
Unknown	2,686 (0.4)	1,063 (0.4)	1,623 (0.4)
Attributed cause of ESKD			
Diabetes	299,371 (47.3)	128,299 (48.4)	171,072 (46.6)
Hypertension	182,703 (28.9)	74,009 (27.9)	108,694 (29.6)
Glomerulonephritis	45,018 (7.1)	20,394 (7.7)	24,624 (6.7)
Cystic Kidney Disease	16,243 (2.6)	7,481 (2.8)	8,762 (2.4).
Other Cause	68,487 (10.8)	26,849 (10.1)	41,638 (11.3)
Unknown	20,702 (3.3)	8,191 (3.1)	125,11 (3.4)
Pre-ESKD nephrology care			
Yes	409,963 (64.8)	174,296 (65.7)	235,667 (64.2)

No	119,699 (18.9)	47,668 (18.0)	72,031 (19.6)
Unknown	102,862 (16.3)	43,259 (16.3)	59,603 (16.2)
Patient informed of transplant as treatment option			
Yes	527,305 (83.4)	220,565 (83.2)	306,740 (83.5)
No	80,813 (12.8)	34,575 (13.0)	46,238 (12.6)
Unknown	24,406 (3.8)	10,083 (3.8)	14,323 (3.9)
Comorbidities			
Obesity (BMI >35 kg/m^2)	121,090 (19.1)	62,431 (23.5)	58,659 (16.0)
Congestive heart failure	173,511 (28.0)	74,617 (28.6)	98,894 (27.5)
Atherosclerotic heart disease	78,658 (12.7)	28,928 (11.1)	49,733 (13.8)
Cerebrovascular disease	52,646 (8.5)	22,967 (8.8)	29,679 (8.2)
Peripheral vascular disease	56,865 (9.0)	21,241 (8.0)	35,624 (9.7)
Other cardiac disease	123,457 (19.9)	48,494 (18.6)	74,963 (20.8)
Hypertension	545,526 (86.3)	229,514 (86.5)	316,012 (86.0)
Diabetes	369,596 (58.4)	158,402 (59.7)	211,194 (57.5)
Chronic obstructive pulmonary disease	56,497 (9.1)	25,453 (9.8)	31,044 (8.6)
Cancer	42,962 (6.9)	16,433 (6.3)	26,529 (7.4)
Tobacco use	40,432 (6.5)	14,387 (5.5)	26,045 (7.2)
Alcohol dependence	10,321 (1.6)	2,207 (0.8)	8,114 (2.2)
Unknown	11,709 (1.9)	4,543 (1.7)	7,166 (2.0)
Dialysis modality			
Hemodialysis	551,127 (87.1)	231,047 (87.1)	320,080 (87.1)
Peritoneal dialysis	64,853 (10.3)	27,081 (10.2)	37,772 (10.3)
Unknown	16,544 (2.6)	7,095 (2.7)	9,449 (2.6)
Primary health insurance status			
Employer	112,814 (17.8)	42,504 (16.0)	70,310 (19.1)
Medicaid	164,793 (26.1)	80,779 (30.5)	84,014 (22.9)
Medicare	271,442 (42.9)	110,940 (41.8)	160,502 (43.7)
Other	41,996 (6.6)	15,547 (5.9)	26,449 (7.2)
None	29,882 (4.7)	10,945 (4.1)	18,937 (5.2)
Unknown	11,597 (1.8)	4,508 (1.7)	7,089 (1.9)
Neighborhood-level characteristics			
Urban	589,085 (93.1)	246,888 (93.1)	342,197 (93.2)
Average % high school graduates Median (IQR)	88.7 (82.4-93.1)	88.3 (82.0-92.8)	89.0 (82.6-93.3)
Average % Female population Mean ± SD	50.8 ± 3.0	50.9 ± 3.0	50.8 ± 3.0
Average % Black population Median (IQR)	7.4 (2.1-23.8)	8.3 (2.2-26.4)	6.9 (2.0-22.0)
Neighborhood poverty level			
< 20% (Low poverty)	477,476 (75.5)	195,787 (73.8)	281,689 (76.7)
≥ 20% (High poverty)	148,754 (23.5)	66,936 (25.2)	81,818 (22.3)

Data are N (%) unless specified otherwise **|** Abbreviations: End-stage kidney disease (ESKD). End-stage renal disease (ESRD), body mass index (BMI), interquartile range (IQR), standard deviation (SD) **|** Missing Data: Rural status (307, <0.1%), neighborhood poverty level (6,294, 1.0%), average % high school (6,186, <0.1%), average % female population (6,179, <0.1%), average % Black population (6179, <0.1%).

Baseline characteristics by outcome

There were 116,820 (18.5%) patients in our study cohort that were waitlisted for a kidney transplant, **Supplemental Table 1.** Waitlisted patients were more likely to be men, younger, receive pre-ESKD nephrology care, have glomerulonephritis as their attributable cause of ESKD, be on peritoneal dialysis, have employer health insurance, and live in a neighborhood with low poverty compared to the overall study cohort, **Supplemental Table 2**. There were 287,170 (45.4%) patients in our study cohort that died before they could be waitlisted, **Supplemental Table 1.** Patients who died were more likely to be women, older, non-Hispanic White, have diabetes as their attributable cause of ESKD, not be informed of transplant as a treatment option, have any comorbidities (with the exception of obesity), be on hemodialysis, and have Medicare as their primary health insurance compared to the overall study cohort, **Supplemental Table 2**.

Table 2. Distribution of sex of ESKD patients who initiated KRT between 1/1/2015 and 12/31/2019 by ESRD Network (N=632,524)

		Patient Sex	
	Overall	**Women**	**Men**
	632,524	265,223 (41.9%)	367,301 (58.1%)
ESRD Network, n (%)			
1 (CT, MA, ME, NH, RH, VT)	20,070 (3.2)	7,895 (39.3)	12,175 (60.7)
2 (NY)	38,860 (6.1)	15,572 (40.1)	23,288 (59.9)
3 (NJ)	18,857 (3.0)	7,541 (40.0)	11,316 (60.0)
4 (DE, PA)	26,436 (4.2)	10,820 (40.9)	15,616 (59.1)
5 (DC, MD, VA, WV)	35,561 (5.6)	15,277 (43.0)	20,284 (57.0)
6 (GA, NC, SC)	56,500 (8.9)	25,078 (44.4)	31,422 (55.6)
7 (FL)	43,582 (6.9)	17,414 (40.0)	26,168 (60.0)
8 (AL, MS, TN)	34,564 (5.5)	15,516 (44.9)	19,048 (55.1)
9 (IN, KY, OH)	46,122 (7.3)	19,720 (42.8)	26,402 (57.2)
10 (IL)	26,856 (4.3)	11,366 (42.3)	15,490 (57.7)
11 (MI, MN, ND, SD, WI)	38,108 (6.0)	16,005 (42.0)	22,103 (58.0)
12 (IA, KS, MO, NE)	23,386 (3.7)	9,860 (42.2)	13,526 (57.8)
13 (AR, LA, OK)	26,226 (4.2)	11,790 (45.0)	14,436 (55.0)
14 (TX)	61,420 (9.7)	26,473 (43.1)	34,947 (56.9)
15 (AZ, CO, NM, NV, UT, WY)	32,652 (5.2)	12,979 (39.8)	19,673 (60.3)
16 (AK, ID, MT, OR, WA)	19,628 (3.1)	7,931 (40.4)	11,697 (59.6)
17 (Northern CA, HI)	31,832 (5.0)	12,937 (40.6)	18,895 (59.4)
18 (Southern CA)	51,864 (8.2)	21,049 (40.6)	30,815 (59.4)

Data are N (%) unless specified otherwise

Abbreviations: End-stage kidney disease (ESKD), end-stage renal disease (ESRD)

Cumulative Incidence of Waitlisting and Death by Sex and ESRD Network

Over a median follow-up time of 2.3 years, the cumulative incidence of waitlisting for men and women at the end of the study period was 22.4% and 18.5%, respectively, **Figure 8**. The median follow-up time among those waitlisted was shorter in women than in men (Median (IQR): 206 (1-583) and 254 (1-621) days, respectively), **Table 3**.

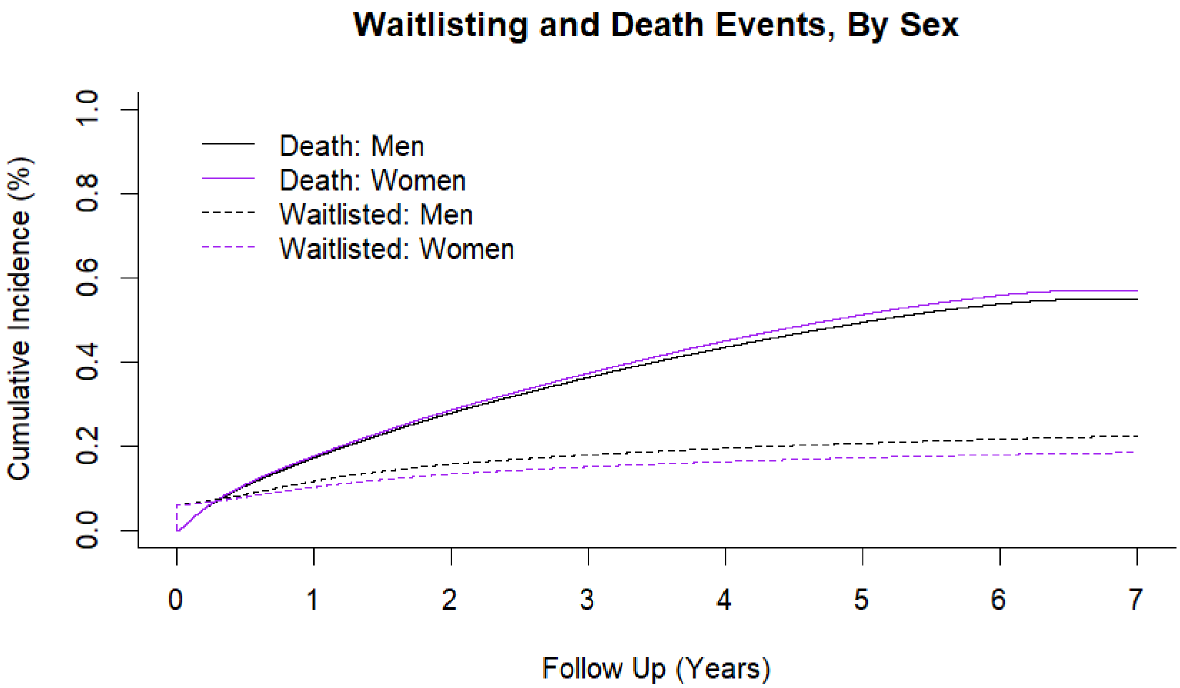
The cumulative incidence of death was slightly greater in women vs men with 57% vs. 55% of the study population dying before getting waitlisted, respectively, **Figure 8**. These patterns were similar across ESRD networks, **Figure 9**.

Table 3. Median (IQR) Follow-Up Time, in days, to waitlisting and death among individuals who were waitlisted or died by sex and ESRD Network, 2015-2019 with follow-up until 2021

	Waitlisted *n = 116,820*		**Died Before Waitlisted** *n = 287,170*	
	Women	Men	Women	Men
Overall	206 (1-583)	254 (1-621)	537 (197-1002)	527 (196-986)
ESRD Network				
1 (CT, MA, ME, NH, RH, VT)	60 (1-408)	108 (1-458)	537 (193-1002)	531 (196-975)
2 (NY)	123 (1-533)	183 (1-532)	513 (180-994)	501 (177-952)
3 (NJ)	174 (1-569)	248 (1-601)	476 (160-964)	482 (152-945)
4 (DE, PA)	95 (1-454)	148 (1-453)	489 (168-961)	493 (190-945)
5 (DC, MD, VA, WV)	170 (1-563)	241 (1-600)	529 (193-1001)	513 (183-963)
6 (GA, NC, SC)	282 (1-651)	319 (1-692)	554 (203-1034)	551 (214-1000)
7 (FL)	303 (1-707)	344 (1-714)	518 (194-984s)	507 (179-955)
8 (AL, MS, TN)	359 (1-717)	398 (101-766)	560 (211-1018)	528 (196-989)
9 (IN, KY, OH)	202 (1-591)	256 (1-616)	503 (178-962)	498 (180-942)
10 (IL)	238 (1-637)	319 (1-716)	480 (169-941)	494 (171-959)
11 (MI, MN, ND, SD, WI)	1 (1-392)	81 (1-450)	511 (191-972)	520 (198-977)
12 (IA, KS, MO, NE)	175 (1-549)	223 (1-573)	525 (190-965)	528 (209-976)
13 (AR, LA, OK)	293 (1-647)	330 (27-663)	542 (214-969)	544 (211-999)
14 (TX)	312 (1-695)	328 (60-700)	567 (221-1037)	571 (224-1033)
15 (AZ, CO, NM, NV, UT, WY)	150 (1-488)	223 (1-585)	592 (229-1049)	550 (217-1011)
16 (AK, ID, MT, OR, WA)	122 (1-518)	201 (1-582)	557 (222-1030)	547 (227-1018)
17 (Northern CA, HI)	126 (1-433)	168 (1-488)	592 (231-1056)	560 (208-1018)
18 (Southern CA)	329 (1-706)	377 (56-747)	572 (206-1049)	554 (200-1039)

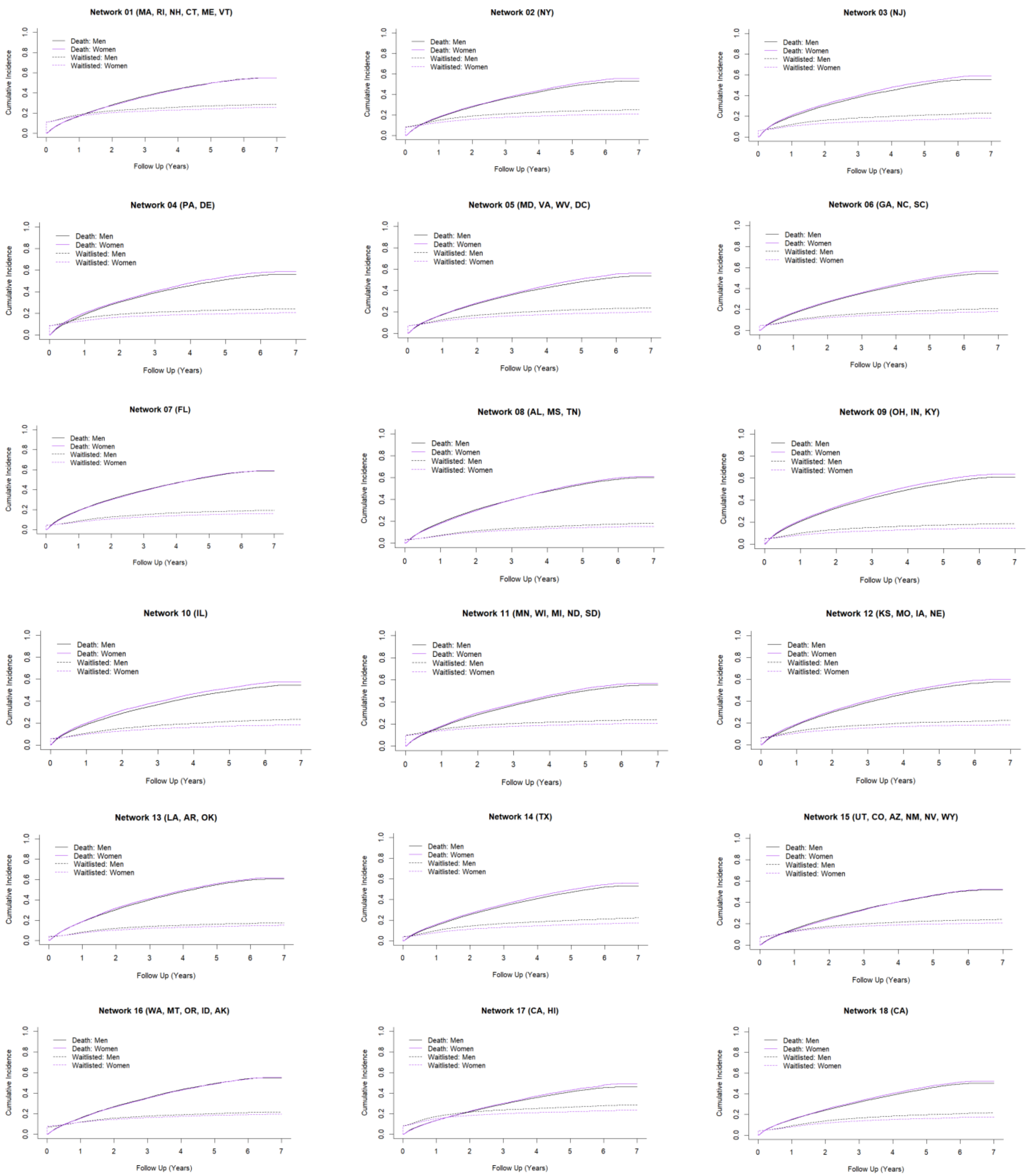
Data are median (IQR) unless specified otherwise
Abbreviations: end-stage renal disease (ESRD)

Figure 8. Cumulative incidence of waitlisting and death among men and women initiating KRT



	Follow Up (Years)						
	1	2	3	4	5	6	7
Waitlisted (%)							
Women	10.3	13.5	15.2	16.4	17.4	18.1	18.5
Men	11.8	15.8	18.1	19.6	20.8	21.8	22.4
Died (%)							
Women	17.8	28.6	28.6	45.1	51.3	55.9	57.0
Men	17.3	27.9	27.9	43.6	49.5	53.8	54.9

Figure 9. Cumulative incidence of waitlisting and death, by sex and ESRD Network



Association between sex, ESRD network, and waitlisting

Overall, women were 17% less likely to be waitlisted versus men (crude HR: 0.83 [0.82, 0.84]), **Table 4**. Patterns were similar in the partially- and fully- adjusted multivariable models (0.82 [0.81, 0.83] and 0.87 [0.86, 0.89], respectively, **Table 4**. The sex disparity in waitlisting was observed across all ESRD networks with some variation in magnitude. The greatest disparity was seen in Network 14 (Texas) (crude HR: 0.78 [0.75, 0.81]) and lowest in Network 16 (AK, ID, MT, OR, WA) (crude HR: 0.90 [0.85, 0.97]), **Table 4** & **Figure 10**. Other hot spots for this disparity were Network 13 (NJ) and Network 9 (OH, KY, IN) (crude HRs: 0.79 [0.73, 0.84] and 0.79 [0.75, 0.83], respectively), **Table 4** & **Figure 10**.

After adjusting for clinical factors, the sex disparity persisted in all 18 ESRD Networks but decreased in magnitude, **Table 4**. The greatest disparities were seen in Networks 3 (NJ), 7 (FL), and 14 (Texas) in the partially adjusted model (0.83 [0.77, 0.89], 0.86 [0.82, 0.90], and 0.84 [0.81, 0.88], respectively) and the lowest were in Networks 6 (GA, NC, SC) and 16 (AK, ID, MT, OR, WA) (0.95 [0.91, 0.99] and 0.95 [0.89, 1.02], respectively), **Table 4**. After adjusting for both clinical and non-clinical factors, the sex disparity persisted in all ESRD Networks, **Table 4.** Hot spots with the greatest disparities in the fully adjusted model included Networks 3 (NJ) and 7 (FL) (0.81 [0.75, 0.88] and 0.83 [0.79, 0.88], respectively), and the lowest were in Networks 6 (GA, NC, SC) and 8 (AL, MS, TN) (0.95 [0.91, 0.99] and 0.98 [0.92, 1.04], respectively), **Table 4**.

Table 4. Association between sex and waitlisting, overall and by ESRD Network, among individuals initiating KIRT between 2015 and 2019 with follow-up through December 31, 2021

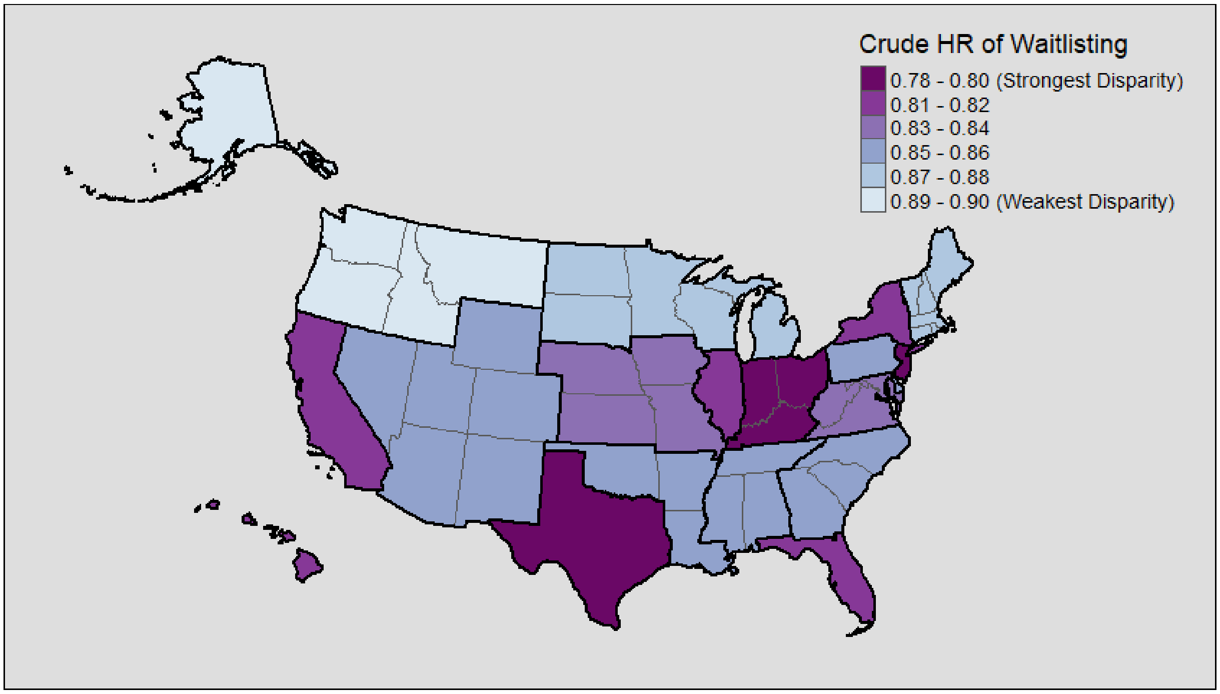
	Women to Men patient HRs		
	Crude HR (95% CI)	**Partially Adjusted HR (95% CI)[1]**	**Fully Adjusted HR (95% CI)[2]**
Overall	0.83 (0.82, 0.84)	0.90 (0.89, 0.91)	0.87 (0.86, 0.89)
ESRD Network			
1 (CT, MA, ME, NH, RH, VT) *n= 20,070 (3%)*	0.88 (0.83, 0.93)	0.91 (0.86, 0.96)	0.87 (0.82, 0.93)
2 (NY) *n= 38,860 (6%*)	0.82 (0.79, 0.86)	0.90 (0.86, 0.94)	0.87 (0.83, 0.91)
3 (NJ) *n= 18,857 (3%)*	0.79 (0.73, 0.84)	0.83 (0.77, 0.89)	0.81 (0.75, 0.88)
4 (DE, PA) *n= 26,436 (4%)*	0.85 (0.80, 0.89)	0.92 (0.87, 0.97)	0.89 (0.83, 0.94)
5 (DC, MD, VA, WV) *n= 35,561 (6%)*	0.83 (0.79, 0.87)	0.93 (0.88, 0.97)	0.90 (0.85, 0.94)
6 (GA, NC, SC) *n= 56,500 (9%)*	0.86 (0.83, 0.90)	0.95 (0.91, 0.99)	0.95 (0.91, 0.99)
7 (FL) *n= 43,582 (7%)*	0.82 (0.78, 0.86)	0.86 (0.82, 0.90)	0.83 (0.79, 0.88)
8 (AL, MS, TN) *n= 34,564 (6%)*	0.85 (0.81, 0.90)	0.93 (0.88, 0.99)	0.98 (0.92, 1.04)
9 (IN, KY, OH) *n= 46,122 (7%)*	0.79 (0.75, 0.83)	0.89 (0.84, 0.93)	0.87 (0.82, 0.92)
10 (IL) *n= 26,856 (4%)*	0.81 (0.77, 0.86)	0.93 (0.88, 0.98)	0.89 (0.83, 0.95)
11 (MI, MN, ND, SD, WI) *n= 38,108 (6%)*	0.87 (0.83, 0.91)	0.93 (0.89, 0.97)	0.90 (0.86, 0.95)
12 (IA, KS, MO, NE) *n= 23,386 (4%)*	0.83 (0.79, 0.89)	0.90 (0.84, 0.95)	0.88 (0.82, 0.94)
13 (AR, LA, OK) *n= 26,226 (4%)*	0.85 (0.80, 0.91)	0.92 (0.86, 0.98)	0.86 (0.80, 0.92)
14 (TX) *n= 61,420 (10%)*	0.78 (0.75, 0.81)	0.84 (0.81, 0.88)	0.85 (0.81, 0.88)
15 (AZ, CO, NM, NV, UT, WY) *n= 32,652 (5%)*	0.86 (0.82, 0.91)	0.91 (0.87, 0.96)	0.88 (0.83, 0.93)
16 (AK, ID, MT, OR, WA) *n= 19,628 (3%)*	0.90 (0.85, 0.97)	0.95 (0.89, 1.02)	0.89 (0.83, 0.96)
17 (Northern CA, HI) *n= 31,832 (5%)*	0.82 (0.78, 0.86)	0.90 (0.85, 0.94)	0.87 (0.83, 0.91)
18 (Southern CA) *n= 51,864 (8%)*	0.81 (0.78, 0.85)	0.91 (0.87, 0.95)	0.88 (0.84, 0.92)

Abbreviations: CI, confidence interval; ESRD: End-stage renal disease; HR: Hazard ratio; KRT: kidney replacement therapy

[1]Adjusted for age, attributed cause of kidney failure, and presence of comorbidities (diabetes, hypertension, peripheral vascular disease, congestive heart failure, other cardiac disease, cerebrovascular disease, atherosclerotic heart disease, chronic obstructive pulmonary disease, tobacco use, alcohol dependence, cancer, obesity)

[2]Adjusted for factors in partial model plus race and ethnicity, pre-failure nephrology care, patient informed of transplant as a treatment option, dialysis modality, primary health insurance status, urban zip code, average % of high school graduates in zip code, average % of female population, average % Black population, and neighborhood poverty level

Figure 10. Geographic variation in sex disparities in waitlisting rates among individuals initiating KRT in the US between 2015 and 2019, with follow-up through December 31, 2021



Hazard Ratio (HR): Hazard of waitlisting rates in women vs. men (reference). A HR <1 indicates a higher waitlisting rate among men initiating KRT as compared with women

Discussion

In this study, women initiating KRT were 17% less likely to be waitlisted as compared with men. Though this sex disparity appeared to be ubiquitous across the US, the magnitude of this disparity varied from a 10% to 22% decreased likelihood of waitlisting for women vs men with ESKD. Hot spots where this disparity was the greatest were Texas, New Jersey, and the Ohio River Valley, and were lowest in the Pacific Northwest region. Observed sex disparities were not explained by clinical or non-clinical factors, and ESRD regions remained hot spots even after adjustment for several factors that likely mediate the association between sex and waitlisting. This finding therefore suggests a role for other systemic, structural, and policy-level factors that may impact women in a systematically different way to men and be unequally distributed across US regions. Future research is needed to better understand these mechanisms, which may serve as potential targets of future interventions to mitigate sex inequities in transplant and to improve access to this life saving resource for women with kidney failure.

The 2023 study by McPherson et al similarly found that racial disparities in waitlisting rates varied by ESRD Network.[11] Regions with the highest Black versus White racial disparities tended to be areas with a smaller proportion of Black ESKD patients.[11] In this context, inequitable healthcare access to Black patients is likely exacerbated in areas with low proportion of Black ESKD patients where culturally appropriate programs may be less prevalent, and future interventions should be tailored with this in mind.[11] Structural factors that drive this racial disparity in transplant should not presumed to be the same factors that drive geographic variation of sex disparities because system-level experiences of racism or discrimination are not the same even across other racial or ethnic groups. In fact, this study did not find disparities in transplant access when comparing Hispanic and Non-Hispanic ESKD patients, and access to waitlisting was not associated with the proportion of Hispanic ESKD patients in a region like it was for Black ESKD patients.[11] In our study, the distribution of women was consistent across ESRD Networks and so this is unlikely to be the primary explanation of the observed geographical variation in sex-based disparities, suggesting other structural factors are at play.

Outside of transplant, a 2022 study examined how sex disparities in age-adjusted mortality rates of COPD varied by US state.[42] Across two decades, mortality rates declined significantly among men, yet mortality changes were more state dependent among women.[42] Despite the vast differences in disease physiology between COPD and ESKD, both Carlson et al and the current study found similar hot spots of sex-based disparities in Midwestern and Southern regions, suggesting similar underlying mechanisms may be at play. For example, the authors of the COPD study hypothesized that a delayed decline in cigarette smoking among women versus men,[42] and a higher proportion of women engaging in other unhealthy lifestyle choices in these regions compared to others, may be driving the geographic variability observed. This theory, as it stands, would put women residing in these regions at a disproportionate risk of experiencing poorer health outcomes, which may include ESKD. However, we adjust for clinical factors in our study, including smoking, and show that women still have reduced access to transplant across all regions, suggestion factors like provider bias, or other structural factors are likely more important for understanding the current study. It is also important to note that the public health implications of the Carlson et al study included a push for resources to be allocated towards precise COPD prevention programs that promote smoking cessation.[42] By the time individuals with CKD progress into ESKD, it is unlikely that focusing on behavior change programs in this group is likely to have a large influence on transplant access.. Rather, given the complex care needs of patients with ESKD, policies and or interventions to promote timely referral, reduce provider bias, and overcome patient-level barriers to transplant are more likely to be effective in this population.[7]

The varying magnitude of sex disparities by ESRD Network does not appear to be explained by different risk profiles of women in different regions as adjustment for these factors did not attenuate associations. In a review of sex disparities in transplant, Melk et al., emphasized that socially-derived factors are likely to outweigh the biological effect in explaining observed sex disparities.[29] For example, US states tend to have different regulations that determine what type of care is covered by Medicaid.[46] Women, who in our cohort were more likely to have Medicaid as their primary health insurance compared to men, may experience reduced access to healthcare due to economic barriers that varies by region. Despite Medicare coverage for all patients initiating KRT, these benefits do not kick in until 90 days after KRT start,[47] and studies consistently show that despite somewhat 'uniform insurance' in this population, those with private insurance have better transplant access,[14,15,46] pointing to broader socioeconomic factors driving these associations. It is also possible that the political climate of where a person lives could serve as a greater barrier for women seeking transplant in some regions verses others. For example, red states in the US, those considered more conservative, may be more likely to uphold traditional gender roles.[48] In this setting, women would more likely have a caregiving burden,[49] fears or concerns about accessing healthcare,[34] or lack the social support needed to pursue transplant as a treatment option,[35] factors previously shown to impact women greater than men.[24] Access to healthcare may also be a proxy serving to represent other indicators of structural barriers related to neighborhood-level safety, food access, poverty, or social interactions.[38,50] Women are more adversely impacted by poor social factors,[51] and in this context it's possible that women with ESKD living in regions with higher proportions of poor social factors may face more significant barriers to transplant. Examining sex disparities among smaller geographic units than ESRD network (e.g., counties) may be able to shed more light on specific neighborhood factors contributing to disparities.

Future Direction and Clinical or Public Health Implications

There are important implications to the findings of this study. First, the finding that sex disparities vary by geography suggests that future interventions should target regions where these disparities are greatest. Importantly, such interventions would need to be multifactorial and multi-level. Choosing the right transplant program is an important decision and can impact the transplant experience based on how a program fits the specific needs or circumstance of a patient.[52] This is especially true when factoring in that the ability to be listed at multiple transplant centers, the number of evaluations insurance will cover, and the option of having multiple programs to choose from vary by the patient and by region.[52] The variation across transplant programs on their requirements, practices, and availability of patient-specific resources is a reason why sex disparities can vary.[52] Some transplant programs are more influenced by gender biases compared to other programs, which could impact the number of women deemed to be ineligible transplant candidates. This implies that increasing transparency and standardization of transplant process requirements and practices is a necessity to alleviating sex disparities in transplant access across the nation. At the patient-level, women would be more equipped with the adequate tools or information needed to choose the right care based on their unique circumstances. However, there is a lack of information being collected at early steps in the transplant process that start in dialysis facilities that would is necessary to measuring access to transplant and the presence of sex-based disparities.[52] Transplant center providers could better support their patients through increasing outreach to nearby dialysis facilities and ensuring that important, pre-transplant information regarding patients is being shared amongst these healthcare facilities.[52] This communication would allow for providers to notice what common characteristics are seen disproportionately among women with ESKD and better center their decision-making with this in mind. While transparency can help patients who are able to choose between various programs based on their fit, some patients do not have this liberty. Therefore, to ensure that sex disparities do not vary by geography or transplant center, health systems must require a standardization of patient-centered decision making and allocate the appropriate resources to support providers in this endeavor. Women with ESKD in this context could be reassured that their transplant eligibility, outcomes, and general decision-making at their transplant program would be similar to other programs since they would all have standardized approaches to transplant care. At the policy level, governing bodies, such as CMS, OPTN, or the United Network for Organ Sharing (UNOS), should regulate and increase the scope of requiring transplant program transparency and standardization.[52] Specifically, the information captured at dialysis facilities and transplant centers should be expanded to include characteristics that can be used as proxies for researchers to measure experiences of sexism or inequitable access to care among women with ESKD. This would help determine precise hot spots of sex disparities across regions or between transplant programs. In fact, collecting this information earlier in the transplant process at dialysis facilities could also confirm where on the transplant care continuum sex disparities are the strongest and most influential.

Nationally, it is important to raise awareness among stakeholders, including patients, providers, advocacy groups, and oversight bodies such as OPTN, CMS, and UNOS that this disparity exists, that it is ubiquitous across the US, and that it is unjust. Addressing biases within the system will be an important step in alleviating sex disparities in transplant and improving access to lifesaving transplant for women with ESKD.

Strengths and Limitations

The key strength of this study is the use of a national registry (i.e., USRDS) that includes all individuals initiating KRT in the United States. Further, using the CMS2728 Medical Evidence form, we were able to account for several clinical and neighborhood-level factors at KRT initiation with minimal missing data across these covariates. However, this study also has limitations. First, our study is limited to interpretations of provider-perceived sex as is captured on the CMS-2728 Medical Evidence form. Second, we used a relatively large geographic catchment area (i.e., ESRD network) to examine geographic variability, for which there is likely variation within each ESRD network that we were unable to capture. Owing to the relatively rare outcome of both ESKD and subsequent waitlisting, this was the smallest geographic unit with adequate power to examine geographical variation in sex disparities. Future studies may consider grouping data across a longer time period to ensure adequate power at smaller geographic catchment areas such as state or county. Finally, this study was limited to data captured in USRDS and it is likely that residual confounding remained.

Conclusion

Women with ESKD remain approximately 17% less likely to be waitlisted for lifesaving kidney transplants as compared to men, and the magnitude of this disparity varies across the US with ‘hotspots’ identified in Texas, New Jersey, and the Ohio River Valley. Future research may prioritize investigating the specific policy-, cultural-, and social-factors occurring at the local level that may be influencing higher sex disparities in some regions as compared with others.

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Supplementary Material

Supplementary Table 1. Waitlisting and death events among ESKD patients who initiated kidney replacement therapy between 1/1/2015 and 12/31/2019, followed through 12/31/2021

ESKD Patient Characteristics	Overall	Waitlisted	Died Before Waitlisted
	632,524	116,820 (18.5%)	287,170 (45.4%)
Sex			
Women	265,223 (41.9)	44,023 (37.7)	122,878 (42.8)
Men	367,301 (58.1)	72,797 (62.3)	164,292 (57.2)
ESRD Network			
1 (CT, MA, ME, NH, RH, VT)	20,070 (3.2)	5,058 (4.3)	9,032 (3.2)
2 (NY)	38,860 (6.1)	8,355 (7.2)	17,265 (6.0)
3 (NJ)	18,857 (3.0)	3,517 (3.0)	8,949 (3.1)
4 (DE, PA)	26,436 (4.2)	5,584 (4.8)	12,658 (4.4)
5 (DC, MD, VA, WV)	35,561 (5.6)	7,038 (6.0)	15,939 (5.6)
6 (GA, NC, SC)	56,500 (8.9)	9,611 (8.2)	25,198 (8.8)
7 (FL)	43,582 (6.9)	6,920 (5.9)	20,858 (7.3)
8 (AL, MS, TN)	34,564 (5.5)	5,083 (4.4)	17,056 (5.9)
9 (IN, KY, OH)	46,122 (7.3)	7,023 (6.0)	23,893 (8.3)
10 (IL)	26,856 (4.3)	5,009 (4.3)	12,418 (4.3)
11 (MI, MN, ND, SD, WI)	38,108 (6.0)	7,916 (6.8)	17,493 (6.1)
12 (IA, KS, MO, NE)	23,386 (3.7)	4,367 (3.7)	11,288 (3.9)
13 (AR, LA, OK)	26,226 (4.2)	3,775 (3.2)	13,133 (4.6)
14 (TX)	61,420 (9.7)	10,571 (9.1)	26,643 (9.3)
15 (AZ, CO, NM, NV, UT, WY)	32,652 (5.2)	6,714 (5.8)	13,581 (4.7)
16 (AK, ID, MT, OR, WA)	19,628 (3.1)	3,667 (3.1)	8,653 (3.0)
17 (Northern CA, HI)	31,832 (5.0)	7,604 (6.5)	11,918 (4.2)
18 (Southern CA)	51,864 (8.2)	9,008 (7.7)	21,195 (7.4)

Data are N (%) unless specified otherwise

Supplementary Table 2. Baseline characteristics of ESKD patients who initiated KRT between 1/1/2015 and 12/31/2019, by waitlisting and death events

ESKD Patient Characteristics	**Overall**	**Waitlisted**	**Died Before Waitlisted**
N (%)	632,524	116,820 (18.5%)	287,170 (45.4%)
Individual-level characteristics			
Sex			
Women	265,223 (41.9)	44,023 (37.7)	122,878 (42.8)
Men	367,301 (58.1)	72,797 (62.3)	164,292 (57.2)
Age (years)			
Median (IQR)	64 (54-73)	54 (43-63)	70 (61-78)
18 – 39	48,606 (7.7)	22,101 (18.9)	7,768 (2.7)
40 – 59	188,134 (29.7)	54,375 (46.6)	55,960 (19.5)
60 – 74	253,778 (40.1)	38,333 (32.8)	123,914 (43.2)
75 – 79	67,114 (10.6)	1,725 (1.5)	43,631 (15.2)
80 - 84	47,873 (7.6)	259 (0.2)	34,515 (12.0)
85 - 90	27,019 (4.3)	27 (0.02)	21,382 (7.5)
Race			
Non-Hispanic White	333,615 (52.7)	57,403 (49.1)	176,371 (61.4)
Non-Hispanic Black	161,107 (25.5)	28,201 (24.1)	63,766 (22.2)
Hispanic	93,541 (14.8)	20,135 (17.2)	32,269 (11.2)
Other	41,575 (6.6)	9,837 (8.4)	14,176 (4.9)
Unknown	2,686 (0.4)	1,244 (1.1)	588 (0.2)
Attributed cause of ESKD			
Diabetes	299,371 (47.3)	43,256 (37.0)	145,025 (50.5)
Hypertension	182,703 (28.9)	29,341 (25.1)	84,244 (29.3)
Glomerulonephritis	45,018 (7.1)	18,509 (15.8)	11,750 (4.1)
Cystic Kidney Disease	16,243 (2.6)	9,404 (8.1)	2,473 (0.9)
Other Cause	68,487 (10.8)	11,234 (9.6)	36,593 (12.7)
Unknown	20,702 (3.3)	1,800 (1.5)	3,524 (1.2)
Pre-ESKD nephrology care			
Yes	409,963 (64.8)	86,663 (74.2)	178,603 (62.2)
No	119,699 (18.9)	15,545 (13.3)	58,294 (20.3)
Unknown	102,862 (16.3)	14,612 (12.5)	50,273 (17.5)
Patient informed of transplant as treatment option			
Yes	527,305 (83.4)	95,788 (82.0)	23,5745 (82.1)
No	80,813 (12.8)	5,093 (4.4)	47,913 (16.7)
Unknown	24,406 (3.8)	15,939 (13.6)	3,512 (1.2)
Comorbidities			
Obesity (BMI >35 kg/m^2)	121,090 (19.1)	16,411 (14.1)	53,465 (18.6)
Congestive heart failure	173,511 (28.0)	11,965 (10.5)	106,417 (37.5)
Atherosclerotic heart disease	78,658 (12.7)	6,533 (5.8)	48,388 (17.1)
Cerebrovascular disease	52,646 (8.5)	3,969 (3.5)	30,762 (10.9)
Peripheral vascular disease	56,865 (9.0)	3,919 (3.5)	35,779 (12.6)
Other cardiac disease	123,457 (19.9)	10,981 (9.7)	74,630 (26.3)
Hypertension	545,526 (86.3)	99,487 (87.6)	246,829 (87.0)

Diabetes	369,596 (58.4)	52,392 (44.9)	18,1085 (63.1)
Chronic obstructive pulmonary disease	56,497 (9.1)	2,201 (1.9)	38,656 (13.6)
Cancer	42,962 (6.9)	3,595 (3.2)	26,800 (9.5)
Tobacco use	40,432 (6.5)	3,667 (3.2)	21,028 (7.4)
Alcohol dependence	10,321 (1.6)	1,381 (1.2)	5,111 (1.8)
Unknown	11,709 (1.9)	3,194 (2.7)	3,532 (1.2)
Dialysis modality			
Hemodialysis	551,127 (87.1)	76,545 (75.7)	267,333 (93.1)
Peritoneal dialysis	64,853 (10.3)	24,548 (24.3)	19,604 (6.8)
Unknown	16,544 (2.6)	15,727 (13.5)	233 (0.1)
Primary health insurance status			
Employer	112,814 (17.8)	46,844 (40.1)	30,822 (10.7)
Medicaid	164,793 (26.1)	23,984 (20.5)	73,049 (25.4)
Medicare	271,442 (42.9)	25,157 (21.5)	159,129 (55.4)
Other	41,996 (6.6)	12,199 (10.4)	13,069 (4.6)
None	29,882 (4.7)	5,480 (4.7)	7,611 (2.7)
Unknown	11,597 (1.8)	3,156 (2.7)	3,490 (1.2)
Neighborhood-level characteristics			
Urban	589,085 (93.1)	110,328 (94.4)	264,834 (92.2)
Average % high school graduates Median (IQR)	88.7 (82.4-93.1)	89.8 (84.6-95.1)	88.9 (83.8-94.1)
Average % Female population Mean ± SD	50.8 ± 3.0	50.8 ± 2.8	50.8 ± 3.0
Average % Black population Median (IQR)	7.4 (2.1-23.8)	6.8 (-2.8-16.4)	6.8 (-3.4-17)
Neighborhood poverty level			
< 20% (Low poverty)	477,476 (75.5)	93,808 (80.3)	217,251 (75.7)
≥ 20% (High poverty)	148,754 (23.5)	21,876 (18.7)	67,137 (23.4)

Data are N (%) unless specified otherwise **|** Abbreviations: End-stage kidney disease (ESKD). End-stage renal disease (ESRD), body mass index (BMI), interquartile range (IQR), standard deviation (SD)