An assessment of renal replacement therapy: A register-based study on equality of access, cost, effectiveness, and cost-effectiveness of kidney transplantation in Sweden

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Abstract

Renal replacement therapy, which includes dialysis and kidney transplantation, is a lifesaving treatment for patients with end-stage renal disease. Kidney transplantation is generally preferred over dialysis as it is associated with lower mortality, higher quality of life, and lower costs. Despite these advantages, the availability of kidney transplant to all who can benefit from it is limited by the scarcity of kidneys. The overall purpose of this thesis was to explore equality of access to kidney transplantation as well as the effectiveness, cost, and cost-effectiveness of kidney transplantation relative to dialysis.

The analyses were performed using data from the Swedish Renal Register, a Swedish national register for renal replacement therapy patients, which was linked to other national registers and regional healthcare utilization databases. Logistic regression models and Cox regression models were applied to study the association between income and education and access to kidney transplantation in general, access to the waitlist, and access to kidney transplantation conditional on waitlist placement. The double robust inverse-probability-weighted regression adjustment approach was applied to estimate the potential outcome mean and the average treatment effect on survival time and healthcare costs.

The results showed that patients with higher income and education had a higher chance of access to kidney transplantation in general than patients with lower income and education. After dividing the kidney transplantation process into access to the waitlist and access to kidney transplantation conditional on waitlist placement, the chance of waitlist access was larger than that of kidney transplantation access conditional on waitlist placement for both higher income and education patients. The survival advantage of kidney transplantation compared with dialysis was around 14 years. There was no significant difference in the survival advantage of kidney transplantation between men and women. Kidney transplantation was not cost-saving in the first year after kidney transplantation, but became cost-saving for the second year, the third year, over the three years, and over lifetime after kidney transplantation.

In conclusion, the findings of this thesis show that there are inequalities related to socioeconomic status in the process of kidney transplantation. Moreover, the inequality in access to the waitlist is substantially larger than the inequality in access to kidney transplantation conditional on waitlist placement, and is therefore expected to contribute more to socioeconomic-status-related inequalities. Kidney transplantation increases survival time and reduces healthcare costs relative to dialysis treatment. This combination of inequality in access and advantage of transplantation over dialysis means that patients with advantageous socioeconomic status will have longer survival time and lower healthcare costs. However, there is no sex inequality in either access to kidney transplantation or survival advantage of kidney transplantation.

Key words: dialysis, kidney transplantation, socioeconomic status, survival time, cost, inequalities

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An assessment of renal replacement therapy

A register-based study on equality of access, cost, effectiveness, and cost-effectiveness of kidney transplantation in Sweden

Ye Zhang

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To my family

Contents

List of papers

This thesis is based on the following original papers, which are referred to in the text by their Roman numerals:

I. Zhang Y, Jarl J, Gerdtham UG. Are there inequities in treatment of end-stage renal disease in Sweden? A longitudinal register-based study on socioeconomic status-related access to kidney transplantation. International Journal of Environmental Research and Public Health 2017; 14(2): 119.

II. Zhang Y, Gerdtham UG, Rydell H, Jarl J. Socioeconomic inequalities in the kidney transplantation process: a registry-based study in Sweden. Transplant Direct 2018; 4(2): e346.

III. Zhang Y, Gerdtham UG, Rydell H, Jarl J. Quantifying the treatment effect of kidney transplantation relative to dialysis on survival time: new results based on propensity score weighting and longitudinal observational data from Sweden. (Submitted.)

IV. Zhang Y, Gerdtham UG, Rydell H, Torbjörn L, Jarl J. Treatment effects of kidney transplantation and dialysis on healthcare costs: new results based on propensity score weighting and real world longitudinal register data from Sweden. (In manuscript.)

Abbreviations

ATE	average treatment effect
CI	confidence interval
DOPPS	International Dialysis Outcomes and Practice Patterns Study
ESRD	end-stage renal disease
HR	hazard ratio
IPWRA	inverse-probability-weighted regression adjustment
KTx	kidney transplantation
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
NA	not available
OR	odds ratio
POM	potential outcome mean
RRT	renal replacement therapy
RTB	Register of the Total Population
RCT	randomized controlled trial
SES	socioeconomic status
SRR	Swedish Renal Register
SEK	Swedish krona
SD	standard deviation

Abstract

Renal replacement therapy, which includes dialysis and kidney transplantation, is a lifesaving treatment for patients with end-stage renal disease. Kidney transplantation is generally preferred over dialysis as it is associated with lower mortality, higher quality of life, and lower costs. Despite these advantages, the availability of kidney transplant to all who can benefit from it is limited by the scarcity of kidneys. The overall purpose of this thesis was to explore equality of access to kidney transplantation as well as the effectiveness, cost, and cost-effectiveness of kidney transplantation relative to dialysis.

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In conclusion, the findings of this thesis show that there are inequalities related to socioeconomic status in the process of kidney transplantation. Moreover, the inequality in access to the waitlist is substantially larger than the inequality in access to kidney transplantation conditional on waitlist placement, and is therefore expected to contribute more to socioeconomic-status-related inequalities. Kidney transplantation increases survival time and reduces healthcare costs relative to dialysis treatment. This combination of inequality in access and advantage of transplantation over dialysis means that patients with advantageous socioeconomic status will have longer survival time and lower healthcare costs. However, there is no sex inequality in either access to kidney transplantation or survival advantage of kidney transplantation.

Introduction

End-stage renal disease and treatments

Kidneys filter wastes and excess fluids from blood, which are then excreted in urine. If the kidneys lose their filtering function, dangerous levels of fluid, electrolytes, and wastes can build up in the body [1]. When the loss of kidney function reaches an advanced state, the result is end-stage renal disease (ESRD), also called end-stage kidney disease, in which the kidneys are no longer able to work as they should to meet the body's needs [1]. ESRD is defined as irreversible kidney damage severe enough that life can be sustained only by dialysis or transplantation; that is, by renal replacement therapy (RRT) [2]. The treatment costs for ESRD patients comprise 1-2% of the total healthcare expenditures in high income countries, representing roughly 0.1% of the general population [3]. The prevalence rate of ESRD in Sweden is 756 per million inhabitants, corresponding to 0.075% of the general population in 2002. This is low from an international perspective, but is the highest among the five Nordic countries [4]. In Sweden, the total cost of ESRD is about 3.1 billion Swedish kronor (SEK) per year [5].

Dialysis therapy includes hemodialysis and peritoneal dialysis. Hemodialysis uses a machine to clean the blood, and can be performed at a dialysis center or at home [6]. Peritoneal dialysis uses the lining of the abdomen (the peritoneum) and a cleaning solution called dialysate to clean the blood; it may be performed at home or even at work if there is a suitable area [7]. It is important to know that dialysis cannot do everything that healthy kidneys do. Therefore, even when patients are on dialysis, they may experience some of the complications of kidney failure [6, 7].

Kidney transplantation (KTx) involves surgery to give the patient a healthy kidney from someone else's body. The new kidney may come from a live donor (usually someone the patient knows) or from a deceased donor [8]. The healthy kidney can do the same job of filtering wastes and excess fluids from the blood that the patient's previous kidneys did when they were healthy [8]. However, KTx is not suitable for every patient (e.g., patients with active infections such as hepatitis), and there are risks associated with this major surgery, such as rejection of the donated kidney.

KTx is generally regarded as the preferred therapy relative to hemodialysis or peritoneal dialysis as it is associated with lower mortality, higher quality of life and

lower costs [9-11]. However, its availability to all who can benefit from it is limited by the scarcity of kidneys [12].

Equality of access to kidney transplantation

Sweden is a country with a publicly-funded universal healthcare system and has no waitlist for ESRD care except for KTx, as assessment and allocation of kidneys are based on numerous factors [4]. Access to KTx involves several steps: (1) a thorough assessment of the patient's physical and psychological fitness for transplantation, along with familial condition (potential living donors); (2) registration on the waitlist with their blood type and tissue type; and (3) allocation of a blood type and tissue type compatible kidney. Access to the waitlist is a key intermediate step in access to KTx. There are four independent transplant centers in Sweden, located in the four largest cities (Stockholm, Gothenburg, Malmö, and Uppsala). These centers all have slightly different policies for allocation of transplants, but all four mainly consider blood group compatibility and time on waitlist, and should not consider socioeconomic status (SES). SES is a theoretical construct encompassing individual, household, and/or community access to resources [13, 14]. It is usually conceptualized as a combination of economic, social, and work status, measured by income, education, and occupation, respectively [13, 14]. There were no changes to the Swedish kidney allocation policy during the period in which data were collected for this thesis (1995–2013). The Swedish healthcare system aims to provide good and equal healthcare for all Swedish citizens. Given the existing lack of kidneys, healthcare providers naturally employ various criteria to prioritize among potential recipients as a means of rationing the limited pool of kidneys [15]. It has long been the tradition in Nordic countries to reduce or even try to eradicate social inequality both in healthcare, where treatment should be given irrespective of SES, and in society at large. Considering the decentralized nature of the Swedish healthcare system and the absence of national guidelines for assessing either eligibility for transplantation or the allocation of kidneys, important questions arise regarding whether there are SES-related priority on access to transplantation [15].

Previous studies, mainly from the USA, have indicated that age, sex, race/ethnicity, SES, marital status, and patient awareness are associated with access to the KTx process [16-25]. The role of SES is complex, because it affects service along the pathway to KTx [26]; for example, higher-SES patients may have better communication with healthcare providers [16]. However, previous studies have mostly used the patient's residential postcode as the only indicator of proxy SES measures. Moreover, these studies have reported inconsistent results regarding SES-related inequalities in access to KTx in general, access to the waitlist, and access to KTx conditional on waitlist placement. For example, studies from the United

Kingdom and France found that patients living in disadvantaged neighborhoods had an equal chance of KTx compared with patients living in advantaged neighborhoods, while a study in the USA found a negative effect of living in disadvantaged neighborhoods [17, 19, 22]. Studies from the USA using education as the indicator of SES found that patients with higher education had a greater chance to be waitlisted and to receive KTx [16, 18]. The International Dialysis Outcomes and Practice Patterns Study (DOPPS), which controlled for income and education at the same time, found that only income was (positively) associated with access to KTx [27]. The most important limitations of previous studies are: (1) income was measured at the area level (postcode or neighborhood poverty) rather than the individual level, and this introduced measurement error which may have led to biased estimates of the effect of income; (2) the DOPPS was the only study to include more than one measure of SES; and (3) the studies included only a subsample of the relevant population or ignored potentially important confounders such as blood type and comorbidities, which may have led to overestimation of the SES effect [16, 17, 22].

Prognosis outcomes of kidney transplantation relative to dialysis

The randomized controlled trial (RCT) is considered the "gold standard" when comparing the outcomes of several interventions or treatments in clinical research, because it allows participants to be randomly (by chance alone) allocated to receive one of several interventions or treatments. Randomization ensures that the two (or more) groups of people in a trial are as similar as possible aside from the intervention or treatment they receive, meaning any between-group differences in outcomes are due solely to the intervention or treatment received. An RCT aims to demonstrate the efficacy of an intervention or treatment while ensuring internal validity by randomly assigning the intervention/treatment [28]. However, external validity is not guaranteed, as the circumstances in specific trials may not be generalizable to a more heterogeneous group of patients treated in a real-world setting [28]. In addition, there are situations in which an RCT may be considered infeasible and unethical; for example, when comparing prognosis between KTx and dialysis. In this case, using observational data from actual medical practice is the most feasible way to compare the treatment effect of KTx relative to dialysis [29]. However, observational data are subjected to treatment selection bias, due to selection based on expected prognosis or other factors that are related to outcomes (e.g. patients with a better prognosis may be more likely to receive KTx over dialysis) and inability to adjust for all relevant patient characteristics [30]. Therefore, important questions arise regarding how to conduct a appropriate

comparison of relative effectiveness between KTx and dialysis by handling the selection bias in observational studies. A traditional approach to the selection problem is by using multivariable regression models. Previous studies from the USA and Sweden applying multivariate Cox regression models to compare the mortality of patients with a KTx or dialysis found that KTx patients had superior long-term survival compared to waitlisted patients on dialysis [9, 31, 32]. Studies from Australia and Norway have shown that KTx seems to confer a survival advantage over dialysis in patients over 60 years or 70 years, respectively [33, 34]. Recently, using a propensity score approach to adjust for selection bias has become increasingly popular [35], and some studies have combined this approach with Cox regression. Sahar et al. [36] used Cox regression analyses stratified by propensity score to show that KTx was associated with improved survival compared to dialysis, and that the benefit of KTx persisted among patients over 60 years. Miklos et al. [37] used Cox regression for propensity score matched patients on dialysis and KTx, and found that the latter was associated with improved survival compared to dialysis in patients over 65 years.

In terms of costs, Stenvinkel et al. found that dialysis cost SEK 600,000 (€68,924) per year while KTx cost SEK 200,000 (€22,975) in the first year and SEK 100,000 (€11,487) in the second [5]. Another study from Sweden also found that 66–79% of the expected healthcare costs over 10 years were avoided through KTx, resulting in a cost saving of €380,000 (in 2012 prices) per patient [38]. However, in order to conduct a fair comparison of cost between KTx and dialysis, it is important to consider treatment selection bias. Patients receiving KTx are usually younger, healthier, and more highly educated than patients receiving dialysis (see Paper II). This may be why most previous studies have compared costs between hemodialysis and peritoneal dialysis by using the propensity score matching approach, because the difference between patients undergoing these two types of dialysis is smaller than that between KTx and dialysis [39, 40]. Studies comparing costs between dialysis and KTx have usually evaluated the costs separately or by using a modeling approach collecting data from published aggregated estimates [41-43], and so there still remains the task of assessing comparable costs between KTx and dialysis. After obtaining comparable survival time and costs for both KTx and dialysis, a simple cost-effectiveness analysis can also be conducted.

Aims and objectives

General aim

The overall aim of this thesis was to explore equality of access to kidney transplantation as well as the effectiveness, cost, and cost-effectiveness of kidney transplantation relative to dialysis.

Specific aims

Four specific aims were developed during the research process:

I.   To study the association between pre-dialysis individual income and education and access to kidney transplantation in general among end-stage renal disease patients (Paper I).

II. To study the association between pre-dialysis individual income and education and access to: (1) waitlist, and (2) kidney transplantation conditional on waitlist placement among end-stage renal disease patients (Paper II).

III. To study the treatment effect of kidney transplantation on survival time compared with dialysis for patients on the waitlist (Paper III).

IV. To study the treatment effect of kidney transplantation on health care costs compared with dialysis for patients on the waitlist (Paper IV).

Contributions to the literature

Relationship between SES and access to kidney transplantation process

Where someone lives, who they are born to, or what work they do should not affect their access to healthcare; this is a particular point of principle in Sweden. Tackling inequity is a key priority for the health service. Before dealing with inequity, the first step is to investigate whether inequalities exist, especially in the healthcare system which aims to provide equal healthcare for all citizens. In order to explore whether SES-related inequalities exist in access to the KTx process, one must first settle on a definition of SES. The main contribution of this thesis is the use of longitudinal register-based individual-level SES measures as two indicators of SES before start of RRT; individual income and education. Previous studies have generally only used one of the three classic indicators of SES, and/or mostly used an area-level measurement (residential postcode or neighborhood poverty) as the only proxy of SES [17, 19, 23, 44]. This introduces measurement error which potentially leads to biased estimation of the effect of individual level income. In addition, we adjusted extensively for both medical and non-medical factors when studying the relationship between individual-level SES and access to the KTx process, which may lead to more accurate estimation of the SES effect than previous studies.

The effects of kidney transplantation on survival time, cost, and cost-effectiveness

Comparing the treatment effects of alternative RRT is an important objective for research into the medical and healthcare services. Nephrologists require valid information on the advantages and disadvantages of alternative treatments if they are to be able to make treatment suggestions and discuss options with their patients. For patients, the most important issue is that treatment decisions are based on reliable information about benefits and harms [45]. Moreover, as healthcare costs are increasing and national resources are limited, healthcare policymakers tasked with deciding how to assign resources are increasingly relying on judgments of both clinical effectiveness and cost-effectiveness, both of which are heavily determined by the estimated survival gains of treatments. The studies included in this thesis estimated the relative and absolute effects of treatments on both survival time and healthcare costs. Previous studies comparing costs between KTx and dialysis have usually evaluated the costs separately or by using a modeling approach with data from published aggregate estimates [41-43]. However, patients receiving KTx are

usually younger, healthier, and more highly educated than patients receiving dialysis (Paper II). While previous studies have mostly focused on the relative risks of alternative treatments, the absolute survival times associated with KTx and dialysis are more intuitive than relative risk, and hence provide quantifiable and meaningful information for non-professional researchers (e.g., patients, physicians, or policy makers) when choosing between alternative treatments. Moreover, absolute survival times also provide a useful basis (comparative survival time and healthcare costs) for economic evaluation of KTx and dialysis in a context that lacks RCTs.

In order to improve comparability of effectiveness in terms of survival time and healthcare costs between KTx and dialysis, it is important to handle the treatment selection bias which comes with observational studies. In the present thesis, this bias is addressed by using a double-robust inverse-probability-weighted regression adjustment (IPWRA) approach. Studies [46, 47] indicate that the propensity score weighting approach is the most general and most efficient technique, because it uses all the available data and does not require any arbitrary decisions with regard to stratification on the propensity score or propensity score matching, as was used in previous studies [36, 37]. In addition, propensity score weighting using the potential outcome framework allows both the relative effect and the absolute effect of alternative treatments to be estimated.

To summarize, this thesis adds to the literature on SES-related inequalities in access to KTx as well as the literature on cost, effectiveness, and cost-effectiveness after KTx by using register-based individual-level data and applying both traditional and advanced methods. The findings provide quantifiable and meaningful information for physicians, patients, and policy makers when choosing between alternative treatments or making relevant policies regarding treatment for ESRD.

Materials and methods

Data sources

This thesis was based on the Swedish Renal Register (SRR) [48], which was linked to several other registers and databases using national personal identification numbers. Table 1 presents the data sources used for the analysis in each paper. The SRR includes Swedish patients referred to a nephrologist and diagnosed with chronic kidney disease, and is a high-quality national register for patients undergoing renal replacement therapy. Data are available from 1991, with almost 100% coverage and a data reporting incidence of 95% [49]. The aim of the SRR is to follow the need for dialysis and KTx after the development of ESRD.

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (Swedish: Longitudinell Integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier, LISA) [50] combines data from several demographic and socioeconomic population registers, including information on income level, country of birth, highest educational level, and occupational status. Since 1990, these data have been updated yearly for all individuals older than 15 years registered in Sweden as of December 31, and since 2010, data for 15-year-old individuals has also been included. LISA provides a basis for longitudinal statistics and research on entire populations, subpopulations, or geographic areas.

The Register of the Total Population (Swedish: Registret över TotalBefolkningen, RTB) [51] is maintained by the government agency Statistics Sweden and provides information on life events including birth, death, marital status, citizenship, family relationships, and migration both within Sweden and to and from other countries. The RTB was initiated in 1968 after a large part of the population data was computerized in 1967 [52], and a complete year-specific version of the RTB is available for each year since 1968 [52]. The quality of RTB data is generally regarded as high. Most data on births, deaths, and civil status are reported by professional and administrative personnel such as midwives, physicians, court officials, and wedding officials [52]. However, quality may be lower when it comes to change of residence within Sweden or migration, as reporting of data in these areas depends on the individual [52].

Scandia Transplant was founded in 1969 and is the organ exchange organization for Denmark, Finland, Iceland, Norway, Sweden, and Estonia. Its purpose is to facilitate the exchange of organs for transplantation between the countries, ensuring that retrieved organs can be given to the right patients. It is owned by the full member hospitals which perform organ transplantation in these countries. All patients waiting for an organ transplant in these countries are listed on one common list for each organ. The Scandia Transplant database [53] thus provides information on waitlist.

The regional healthcare utilization databases provide information on healthcare utilizations and costs for people who live in Region Skåne and Stockholm County Council, which are two healthcare administration areas covering around a third of the Swedish population. Swedish healthcare is organized into three levels: primary care, specialist outpatient care, and inpatient care. Primary care is first-line care and includes general practice services and other specialized services such as child healthcare centers [54]. In specialist outpatient care, patients visit a specialist at hospitals and outpatient clinics, mainly after a referral from primary care [54]. Inpatient care involves care episodes at a hospital upon referral from an outpatient care setting or from the hospital's accident and emergency ward [54].

Figure 1 illustrates the linkage between the SRR and other databases as well as the information provided by each database.

Table 1: Data sources used in Papers I–IV:

	Paper I	Paper II	Paper III	Paper IV
Swedish Renal Register (SRR)	✓	✓	✓	✓
Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)	✓	✓	✓	✓
Register of the Total Population (RTB)	✓	✓	✓	✓
Scandia Transplant database		✓	✓	✓
Regional healthcare utilization databases for Skåne and Stockholm			✓ (in sensitivity analysis)	✓
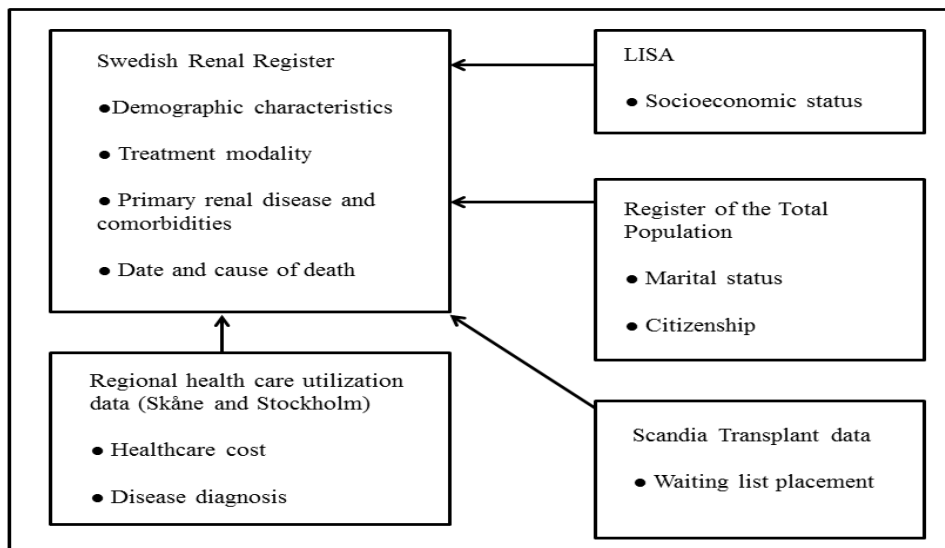
Figure 1:
Data sources and information linked to the Swedish Renal Register.
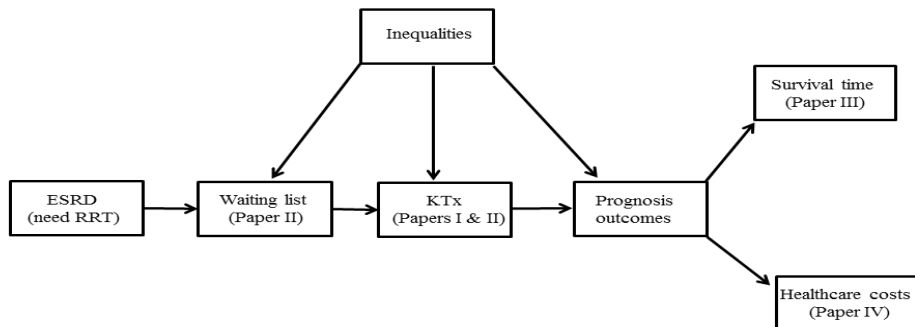
Figure 2:
Outcomes studied in Papers I–IV:

Study populations

The study populations and their characteristics are presented in Table 2, and the outcomes in Figure 2. All four studies included in this thesis focused on adult ESRD patients. Papers I and II explored the association between SES and access to KTx in general and access to the process leading to KTx by adjusting for other potentially confounding variables. Both papers included all adult ESRD patients who started RRT between 1995 and 2013, as recorded in the SRR. Paper I focused on access to KTx in general, including both living and deceased donor transplantation. This sample consisted of 4,392 patients receiving KTx and 11,823 patients receiving dialysis. In Paper II, we separated the outcomes into access to the waitlist and access to KTx conditional on waitlist placement, and used Cox regression to study the association between income and education and these two outcomes. Of the 13,982 patients in the study population, 2,694 were placed on the waitlist and 2,164 received KTx. We excluded patients who received pre-emptive transplantation or living donor transplants and patients who were placed on the waitlist before starting dialysis, because in these cases we did not have the waitlist date information which was needed to calculate the time to waitlist and time to KTx in the Cox analysis. Papers III and IV explored the treatment effect of KTx relative to dialysis, but used different prognosis outcomes. Paper III focused on the survival time after different treatments. Death information was available for all ESRD patients in Sweden, but we excluded patients with missing information on the covariate "home county", which was also included in the treatment model for calculating propensity score. This sample therefore consisted of the 2,676 patients who joined the waitlist, 2,151of whom received KTx. Paper IV focused on the healthcare costs after different treatments. The only healthcare utilization and costs information available was that for Region Skåne and Stockholm between 1998 and 2012, which led to a much smaller sample size. Because some patients had multiple listings/re-transplantations, only the first listing/kidney transplantation was considered in the current analysis.

Table 2 : The study populations and their characteristics in Papers I-IV

	Paper I	Paper II	Paper III	Paper IV
Time period	1995–2012	1995–2012	1995–2012	1998–2012
Total population (n)	16,215	13,982	13,877	952
Waitlist placement (n)	NA	2,694	2,676	223
Kidney transplantation (n)	4,392	2,164	2,151	729
Dialysis (n)	11,823	11,818	11,726	NA
Age (mean±SD)	63.7±15.1	63.7±15.1	52.1±11.3	52.1±11.2
Men (%)	65.4	65.6	66.1	65.1

SD: standard deviation; NA: not available

Socioeconomic status indicators

Papers I and II explored the relationship between SES and access to the KTx process, and SES was also an important confounding factor controlled in Papers III and IV. This thesis used two indicators of SES: individual-level income and education before patients started RRT. Income was defined as the individual disposable income (including income from work and benefits) derived from the household disposable income adjusted for consumption weights [55]. It was adjusted to the 2012 price level using the consumer price index from Statistics Sweden [56], and converted from Swedish krona (SEK) to Euro (€) using the 2012 average exchange rate (€1=SEK8.7053) [57]. Income was divided into quintiles from quintile 1, the most disadvantaged quintile, to quintile 5, the most advantaged quintile. Education was categorized on the basis of the Swedish education system, into mandatory education (≤ 9 years), upper secondary education (9-12 years), and higher education (>12 years). In Sweden, schooling became mandatory for 7 years in the 1930s and for 8 years in the 1950s. Since 1972, Swedish children have had 9 years of mandatory attendance ("grundskola" in Swedish), starting in August of the year the child turns 7 and continuing to June of the year the child turns 16. Following this is an optional 3 years of upper secondary school ("gymnasieskola" in Swedish). After gymnasieskola, students can apply to a university in order to receive a tertiary education.

Ethics

All studies included in this thesis were approved by the Lund Regional Ethical Review Board (ref: 2014/144). The data analyzed in this thesis were de-identified, and were stored in such a way as to ensure that no non-related researchers had access. We did not request informed consent from individual study participants, but provided an opt-out option by advertising our research project in the Swedish newspaper "Dagens nyheter". The data were presented in aggregated form to eliminate the possibility that any specific person could be identified when we published our manuscripts. The data sets analyzed in this thesis are not publicly available, but are available from the corresponding register holders upon reasonable request [58].

Statistical methods

The section presents and discusses some of the key aspects of the statistical methods used for analyzing the data, first in general and then separately for each paper.

Dealing with potential confounders

From a methodological perspective, the ideal strategy for identifying the treatment effect of KTx relative to dialysis would be to randomly assign KTx or dialysis to individual ESRD patients, follow them over their life cycle, and compare the outcomes of interest between them. However, as discussed in the introduction to this thesis, the random assignment design is considered infeasible and unethical in this context. We thus have to rely on observational data, which usually involve non-random selection into treatment and may also contain unobservable bias.

Regarding the issue of selection bias in the observational studies in this thesis, there are usually two selection steps in the process of obtaining KTx: first, patients are selected to join the waitlist; and second, patients on the waitlist are selected to get a transplant. However, patients receiving KTx are generally younger and healthier than waitlisted dialysis patients and general dialysis patients, meaning that differences in outcomes between KTx and dialysis are not just due to the different treatment modalities. The traditional way of dealing with this selection bias is to use multivariate regression models, but recently the propensity score approach has become increasingly popular. The difference between general dialysis patients and KTx patients is larger than the difference between waitlisted dialysis patients and KTx patients [9], and so in order to minimize the selection bias in this thesis we limited ourselves to patients on the waitlist. However, selection bias still exists for waitlist patients, as patients that receive KTx are generally younger and healthier [9], and so we applied the propensity score weighting approach to handle this remaining bias. The propensity score is defined as the probability of receiving KTx or dialysis conditional on measured baseline covariates. A key property of the propensity score approach is that, conditional on the propensity score, treatment assignment is independent of the observed baseline covariates (i.e., differences in outcomes between KTx and dialysis are due solely to the different treatment modalities) [59]. More information about the propensity score weighting approach is given in Paper III. However, neither the multivariate regression method nor the propensity score approach can control for unobservable factors.

As with all analyses of observational data, the major threat to the validity of the results is confounding that based on unmeasured characteristics that may have affected the relationship between RRT modality and outcomes. One possible way of further accounting for any unobserved factors is the instrumental variable

method, which mimics an RCT to a certain extent [60]. The idea is to find an "instrumental" variable which is related to the actual treatment but randomly "allocated" to a patient, so is independent of the patient characteristics that are related to outcomes [60]. The random allocation of this variable can be considered as a "natural experiment" and thus has the advantage of preventing selection bias in the same way as an RCT [60]. Instrumental variable methods have been used in nephrology when investigating the effect of therapy on the outcome [61, 62]; for example, using the percentage of patients with a catheter at a facility as the instrumental variable when studying the relationship between facility hemodialysis vascular access use and mortality. However, those studies only focused on hemodialysis patients. For the studies included in this thesis, a search for the variables we had in the registered datasets revealed difficulties in finding a variable that was (1) related to the treatment assigned; (2) unrelated to the observed and unobserved prognostic factors; and (3) unrelated to outcome except through pathways operating via the individually-assigned treatment [60]. Another possible method is the fixed effect method, but this can only remove bias from unobserved variables which are constant or "fixed" over time, and not from those unobserved variables that vary over time. However, unobserved variables are only a problem if they are correlated with both treatment selection and outcome measure. If an unobserved variable is highly correlated with the controlled observed variables, it should have very little influence on the results with respect to treatment effects. Conversely, if an unobserved variable is not correlated with any controlled observed variables, the results may be affected. In this thesis, the linked database provided a very rich source of information, and we made extensive use of this information in trying to minimize this risk. For example, patients' preferences regarding treatment may also affect the outcomes, and we did not have this information in our database. However, patients' preference is usually related to their SES and we controlled for both individual-level income and education in all four studies, which will have mitigated the problem of unobserved variables.

Paper I

Association between income and education and access to kidney transplantation in general

Paper I examined the association between SES and the probability of receiving KTx, using the traditional univariate and multivariate logistic regression method with different variable clusters being adjusted to show the variation in the association. Logistic regression was used to estimate the odds ratio of receiving KTx. When we explored the association between income and access to KTx, we controlled for education because education can be seen as a factor underlying this association. Education is generally defined early in life, and income is partly the result of

educational achievements. Controlling for this also allowed us to explore which was the stronger independent factor, which might inform inferences about mechanisms. When we explored the association between education and access to KTx, we did not control for income in the education equation, as income is partly the result of educational achievements. We also performed several sensitivity analyses, such as limiting the sample to working-age patients due to concerns that employment status determines treatment choice [63]. Throughout the analyses, we controlled for age, sex, year of starting RRT, marital status, citizenship, primary renal disease, whether the patient's home county had a KTx center, and comorbidities.

Paper II

Association between income and education and access to the waitlist and kidney transplantation conditional on waitlist placement

The waitlist process is a key intermediate step to KTx. In Paper II we therefore explored the association between SES and (1) access to the waitlist; and (2) access to KTx conditional on waitlist placement. The definitions of the SES factors and the controlled confounding factors were the same as in Paper I, except that blood type was also adjusted for patients on the waitlist in this study.

We used univariate and multivariate Cox regression to assess the association between SES and the two outcomes, because this method allowed us to consider both outcome and time to outcome at the same time. Time to waitlist was defined as the time from the start of dialysis to the date of placement on the waitlist. Patients not waitlisted were censored at time of death or at the end of the study. Time to KTx was defined as the time from placement on the waitlist to the date of the KTx. We also ran the same analysis for men and women separately to investigate whether the effects of SES differed by sex. In order to test the robustness of the results from the main analysis, the association between income and the two outcomes was tested by using income 5 years before dialysis and the average income over 5 years before dialysis. The reason for this is that income 1 year before dialysis, as used in the main analysis, runs the risk of capturing patients' reduced health status as a result of the kidney disease as well as their SES, while income 5 years before dialysis and the average income over 5 years before dialysis should be less influenced by the patients' kidney-related health status and should therefore be purer SES measures. The downside of using these measures is that income levels may have changed, meaning that income 5 years before dialysis may not be a good indicator of current SES. However, in order to disentangle the general health and income (SES) effects, we would need to adjust further for general health, which unfortunately is not represented in the current dataset.

Paper III

Treatment effect of kidney transplantation on survival time compared with dialysis

Paper III mainly focused on estimating the treatment effect of KTx on survival time relative to dialysis using the observational data. As mentioned in the section above on potential confounders, the process of obtaining KTx generally includes two selection steps: selection to the waitlist, and then selection from the waitlist to KTx. Some previous studies compared KTx patients with general dialysis patients (including dialysis patients not on the waitlist) while others compared KTx patients with waitlisted dialysis patients. General dialysis patients have a higher mortality rate than waitlisted dialysis patients because the former group includes high-risk patients on dialysis who are not candidates for transplantation [9]. Thus, the previous studies which were limited to patients on the waitlist may have reduced the selection bias. However, limitation to the waitlist cannot completely control for selection bias, as the patients who receive KTx are generally younger and healthier than waitlisted dialysis patients [36]. Some previous studies applied Cox regression analyses combined with propensity score matching or stratification methods to further reduce the selection bias [36, 37]. However, there is evidence [46, 47] indicating that the propensity score weighting approach is the most general and most efficient method, because it uses all available data and does not require any arbitrary decisions with regard to stratification on the propensity score or propensity score matching. In addition, the propensity score weighting method using the potential-outcomes framework permits the estimation of both the relative reduction and the absolute reduction in the survival/costs occurring in a treated population compared with an untreated population.

Both the potential outcome mean (POM) and the average treatment effect (ATE) were estimated in Paper III. The POM for KTx refers to the average survival time if all the patients receive KTx (Y1), while the POM for dialysis refers to the average survival time if all the patients receive dialysis (Y0). The ATE is the difference in average survival time between KTx and dialysis over the whole sample [59]. However, our observational data can only give us Y1 or Y0 (receiving or not receiving KTx) for each patient. When the treatment is assigned randomly, the randomization ensures that the POMs are independent of factors influencing treatment assignment. In observational studies, the treatment is not randomly assigned, and the conditional independence assumption is needed in order to estimate ATE. The conditional independence assumption says that there is no observable bias if the outcome is independent of factors influencing treatment assignment after conditioning on a sufficient number of covariates. We applied the double-robust IPWRA approach, which is a combination of inverse-probability weighting and regression adjustment, to estimate the treatment effects on the prognosis outcomes.

The principles behind regression adjustment and inverse-probability weighting are illustrated in Figures 3 and 4 by using a simple sample. Regression adjustment uses averages of predicted outcomes to estimate the average treatment effect. Treatment assignment is not modeled in this method, but instead is handled by fitting two separate models for KTx and dialysis, respectively, and averaging the predicted outcomes. Figure 3 illustrates an example of regression adjustment. The solid triangles represent kidney transplantation patients and the solid circles represent dialysis patients. We observed that older patients had shorter survival time regardless of their treatment modality (Figure 3a). Regression adjustment fits separate linear regression equations for survival time against patients' age for KTx and dialysis patients by using the observed survival time for KTx or dialysis (Figure 3b), and estimates unobserved potential outcomes (expected survival time for KTx patients if they receive dialysis and expected survival time for dialysis patients if they receive KTx, indicated as hollow triangles and hollow circles in Figure 3b). We can then use the blue regression line to predict each patient's survival time assuming every patient receives KTx, and the green regression line to predict each patient's survival time assuming every patient receives dialysis. The treatment effect for a patient of a particular age is the vertical difference between the blue and green regression line. Based on these counterfactuals, a treatment effect is estimated for each patient and then averaged across the whole sample to get the average treatment effect for the whole population.

An inverse-probability-weighted estimator models treatment assignment and uses weighted averages of the observed outcome to estimate the potential outcomes and the average treatment effect. The weights correct for the unobserved outcomes. The weight for each patient is derived from the predicted probability of getting kidney transplantation, which we denote by Pi. For example, in Figure 4, the relatively older KTx patients (large triangles) will have a relatively lower probability of receiving KTx, and the relatively younger dialysis patients (large circles) who will have a relatively lower probability of getting dialysis, and so both groups are assigned a large weight. Extra weights are given to those older KTx patients and younger dialysis patients that we do observe, in order to compensate for the sparseness of their number in the sample. Specifically, observed dialysis patients are weighted by 1/Pi and KTx patients are weighted by 1/1-Pi. The weights are larger when the probability of dialysis is small among dialysis patients and when it is large among KTx patients [64, 65].

The IPWRA estimator uses weighted regression coefficients to calculate the predicted outcome for each individual in each treatment and then the averaged predicted outcomes for each treatment, where the weights are the estimated inverse probabilities of having each treatment. This means that the more unlikely an observed treatment assignment, the higher the weight given to the observation. The first step estimates the probability of treatment using a logit regression model

including variables that affect treatment assignment and outcomes at baseline. There is a lack of consensus in the literature as to which variables should be included in the propensity score model [66], and so we included as many pre-treatment covariates related to treatment assignment as possible. All the covariates we included have been used in previously published articles related to this topic [36, 67-69]. The second step in the IPWRA method uses regression adjustment analysis with weights provided by the inverse of the estimated probability that a patient received a treatment modality [70]. The weights do not bias the regression adjustment estimator if the treatment model is wrongly specified, providing the outcome model is correct. Similarly, the weights adjust the regression adjustment estimator if the treatment model is appropriate but the outcome model is wrongly specified; that is, the IPWRA is a so-called double-robust method [70]. The double-robustness characteristic means that only the outcome model or the treatment model needs to be correctly specified in order to estimate the POM and ATE. In order to test whether the double-robustness characteristic holds, we used the Hosmer-Lemeshow C statistic and the Pregibon link test [71-73] to assess the goodness of fit and specification of the treatment model. The Hosmer-Lemeshow C statistic evaluates whether the difference between the observed and predicted values of the response variable is significant; failure to reject the null hypothesis of no difference is a signal of good model calibration [73]. The Pregibon link test estimates the treatment-effects equation with the linear predicted value and the squared linear predicted value as the only two explanatory variables (besides a constant). If the treatment equation is correctly specified, the coefficient of the squared linear predicted value should be non-significant [72]. Akaike's information criterion was used to compare the fit of outcome models using different distributions; here, a smaller statistic suggests a better fit [71]. We also used a standardized difference method to assess the balance of baseline covariates between the KTx and dialysis groups in the sample before and after weighting by the inverse probability of treatment (propensity score) [74, 75]. Unlike traditional significance tests such as t-tests and chi-square tests, standardized differences are not influenced by sample size and are useful in identifying meaningful differences. Typically, a standardized difference greater than 0.1 is considered meaningful [75]. We also performed a formal over-identification test for covariate balance after weighting. Curtis [46] notes the necessity of paying careful attention to contraindications to the treatments of interest. In the case where the likelihood of receiving a treatment is zero, the inverse probability-weighted estimation is not an appropriate approach. We therefore evaluated the estimated probabilities to ensure that none of them were either very large (close to 1) or very small (close to 0). The overlap assumption (i.e., that each patient had a positive probability of getting each treatment) was assessed using an overlap plot.
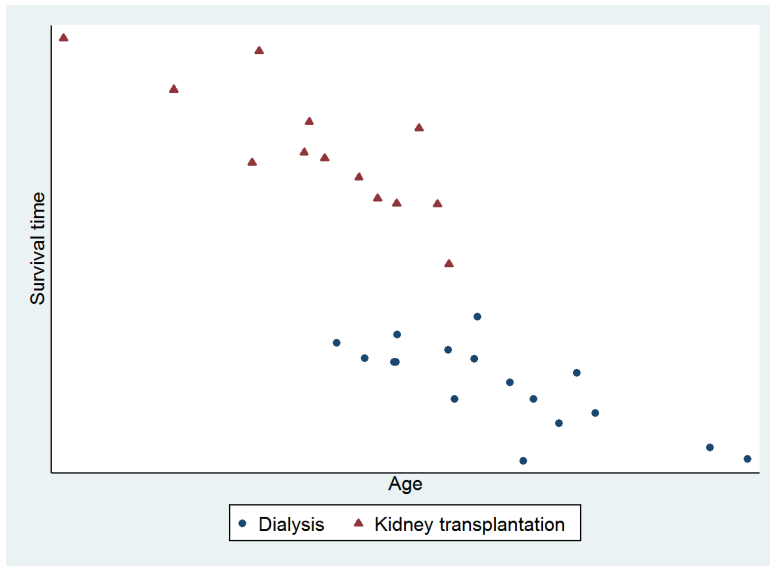
Figure 3a:
Survival time and patients' age by treatment modality
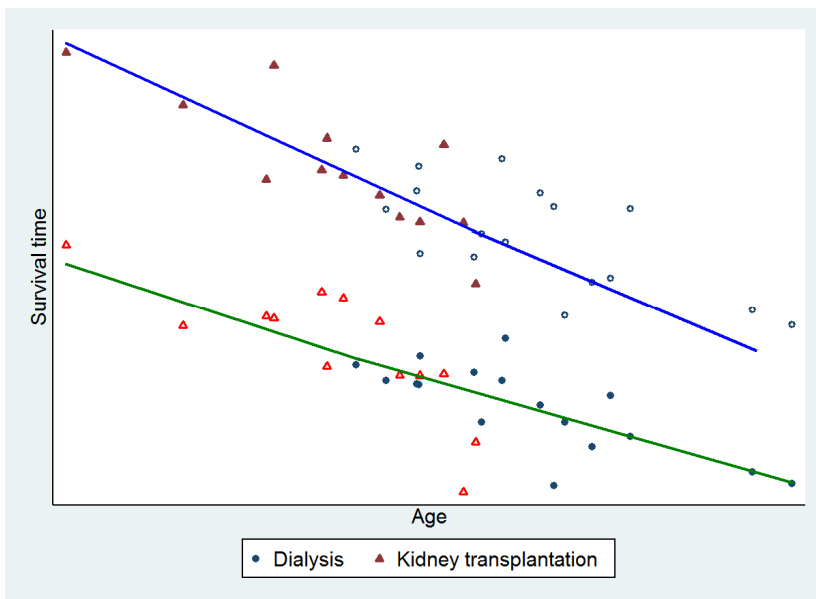
Figure 3b:
Survival time and patients' age by treatment modality and counterfactuals
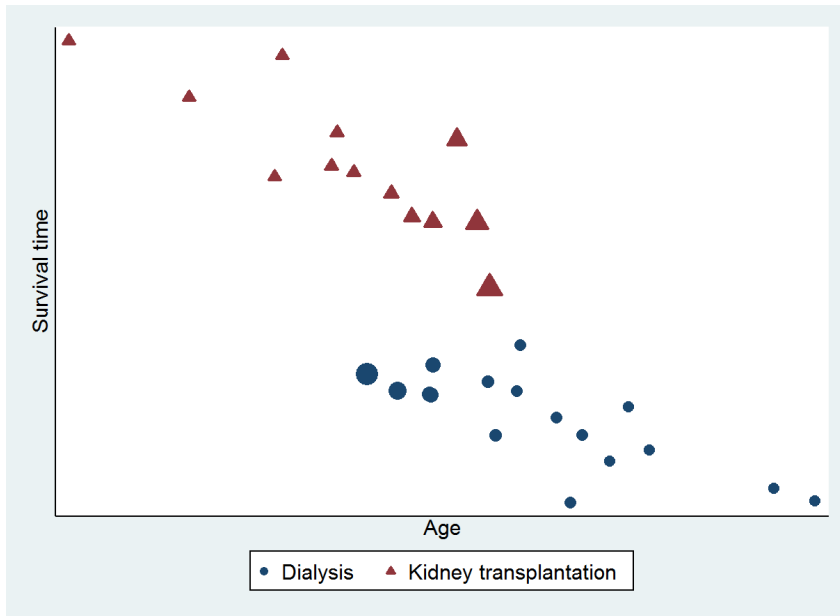
Figure 4:
Inverse-probability-weighted treatment effects estimator

We also estimated the POM and ATE for men and women separately, and then compared the difference of ATE over sex. In our sensitivity analysis, in order to compare our results with the new method to results from previous studies focused on general dialysis patients, we also performed the analysis for a study population of all patients who started RRT between 1995 and 2012, irrespective of waitlist status.

The Charlson comorbidity index (CCI) is a simple and valid method of estimating the risk of death from comorbid diseases. It takes into account both the number and the seriousness of comorbid diseases, and can be calculated by using the diagnoses before start of RRT [76]. In the main analysis we only controlled for those comorbidities registered in the SRR, and we therefore re-ran the analyses including the CCI for both waitlisted patients and the full patient sample. However, the detailed information on prior diagnoses needed for calculating the CCI was only available for a subsample of patients (two health care administrative areas), and therefore the main analysis for this sample was re-run for comparison reasons.

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Paper IV

Treatment effect of kidney transplantation on healthcare costs compared with dialysis

In Paper IV, we estimated the treatment effects on healthcare costs of KTx relative to dialysis using the same IPWRA approach as in Paper III. The primary outcome was total healthcare cost of each year after KTx, defined as total healthcare expenditures of each full year after KTx for each patient up to the third year, calculated from the date of the KTx to one year later and so on. While information on transplant dates was available for patients who received KTx, this was not the case for patients who were still on dialysis. In order to compare the healthcare costs after KTx between KTx and dialysis, we needed to calculate these costs not only for KTx patients but also for dialysis patients on the assumption that they later received KTx. We therefore had to generate a hypothetical "KTx date" for each dialysis patient, in order to match the data structure of the KTx group, before conducting the POM and ATE estimations. For this purpose, the one-to-one nearest neighbor propensity score matching approach was employed. This approach paired the KTx and dialysis patients who were similar in terms of the probability of receiving KTx, estimated by their observable baseline characteristics before the start of RRT [77].

The primary outcome was the total healthcare costs of each full year after KTx up to the third year, total healthcare costs over three years, and total lifetime healthcare costs. We then performed the same analysis for the inpatient costs, and outpatient and primary care costs. Since we have zero total healthcare costs for some patients in the specific year after KTx, we applied both a gamma distribution and a Poisson distribution for the outcome model.

General statistical comments

All statistical analyses in this thesis were performed using version 14.0 of the STATA software package (Stata Corporation, College Station, TX). Statistical significance was set at $p < 0.05$.

Results

The main results of the four papers included in this thesis are given in brief below. Readers are referred to each separate paper for a full presentation of the results.

Paper I

Effects of income and education on access to kidney transplantation in general

Patients in the highest income group had more than three times the likelihood of access to KTx compared with patients in the lowest income group (Table 3). Although the effect size changed when controlling for different variable clusters, there was a clear positive association between income and likelihood of KTx.

Similarly, patients with higher education had more than three times the likelihood of access to KTx compared with patients with only mandatory education in the fully adjusted model (Table 4). Overall, both higher income and higher education increased the likelihood of access to KTx.

Table 3: Association between income and access to kidney transplantation in the multivariate logistic regression

Variables Included in model	Model 1: Crude OR of income (95% CI)	Model 2: Adjusted for education, OR (95% CI)	Model 3: Adjusted for Model 2 + demographic variables, OR (95% CI)	Model 4: Adjusted for Model 3 + clinical variables, OR (95% CI)
Disposable income (ref = quintile 1)				
Quintile 2 (100,002–122,743 SEK)	0.86 * (0.77–0.97)	0.80 *** (0.71–0.90)	1.02 (0.88–1.19)	1.12 (0.95–1.33)
Quintile 3 (122,755–146,224 SEK)	0.87 * (0.78–0.98)	0.77 *** (0.68–0.87)	1.10 (0.94–1.28)	1.21 * (1.03–1.43)
Quintile 4 (146,231–188,732 SEK)	1.44 *** (1.29–1.61)	1.10 (0.98–1.24)	1.79 *** (1.54–2.08)	1.91 *** (1.63–2.24)
Quintile 5 (188,751–6,685,735 SEK)	2.16 *** (1.94–2.40)	1.40 *** (1.25–1.56)	3.23 *** (2.77–3.76)	3.22 *** (2.73–3.80)
Education (ref = mandatory)				
Secondary school		2.80 *** (2.58–3.05)	1.46 *** (1.32–1.62)	1.48 *** (1.32–1.65)
Higher education		4.56 *** (4.11–5.07)	2.47 *** (2.16–2.82)	2.35 *** (2.03–2.72)

Ref : reference group; OR: odds ratio; CI : confidence interval. Model 1: Crude OR of disposable income; Model 2: ORs adjusted for education; Model 3: Model 2 + demographic variables (age, sex, year of first RRT, marital status, citizenship, and home county); Model 4: Model 3 + clinical variables including primary renal disease and comorbidities. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Table 4: Association between education and access to kidney transplantation in the multivariate logistic regression

Variables included in model	Model 1 Crude OR of education (95% CI)	Model 2 Adjusted for demographic variables, OR (95% CI)	Model 3 Adjusted for Model 2 + clinical variables, OR (95% CI)
Education (ref = mandatory)			
Secondary school	2.97 *** (2.73–3.23)	1.67 *** (1.51–1.85)	1.68 *** (1.51–1.88)
Higher education	5.25 *** (4.74–5.81)	3.36 *** (2.96–3.82)	3.18 *** (2.77–3.66)

Ref: reference group; OR:odds ratio; CI: confidence interval. Model 1: Crude OR of education; Model 2: ORs adjusted for demographic variables (age, sex, year of first RRT, marital status, citizenship, and home county); Model 3: Model 2 + clinical variables including primary renal disease and comorbidities. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Paper II

Effects of income and education on access to the waitlist and kidney transplantation conditional on waitlist placement

After separating the outcome into access to waitlist and kidney transplantation conditional on waitlist placement, both higher income and higher education showed a positive effect on both outcomes (Tables 5 and 6). The effect size was larger for

access to waitlist than for access to kidney transplantation, for both higher income and higher education.

When we performed the same analysis for men and women separately, the effects of both income and education on access to the waitlist/KTx were similar to the estimations of the main analysis. Using different income measurements (income 5 years before dialysis or average income over the 5 years before dialysis) changed the effect of income slightly, but the effect remained significant.

Table 5: Association between income and access to the waitlist and kidney transplantation conditional on waitlist placement, by Cox proportional hazard regression

Variables included in the model	Model 1: Crude HR of income (95% CI)	Model 2: Adjusted for education, HR (95% CI)	Model 3: Adjusted for Model 2 + demographic variables, HR (95% CI)	Model 4: Adjusted for Model 3 + clinical variables, HR (95% CI)
Access to the waitlist (n=13,982)				
Disposable income (ref = quintile 1)				
Quintile 2	0.83**	0.80**	0.93	0.99
	(0.73–0.95)	(0.70–0.91)	(0.82–1.06)	(0.87–1.13)
Quintile 3	0.79**	0.72***	0.88	0.97
	(0.69–0.90)	(0.63–0.83)	(0.77–1.01)	(0.84–1.11)
Quintile 4	1.14*	0.93	1.21**	1.29***
	(1.00–1.28)	(0.82–1.05)	(1.07–1.37)	(1.14–1.46)
Quintile 5	1.66***	1.18**	1.76***	1.73***
	(1.48–1.86)	(1.05–1.32)	(1.56–1.99)	(1.53–1.96)
Education (ref = mandatory)				
Secondary school		2.03***	1.28***	1.25***
		(1.86–2.22)	(1.17–1.40)	(1.14–1.37)
Higher education		2.99***	1.97***	1.82***
		(2.68–3.34)	(1.76–2.20)	(1.63–2.04)
Access to kidney transplantation conditional on waitlist placement (n=2,694)				
Disposable income (ref = quintile 1)				
Quintile 2	1.14	1.14	1.17*	1.22**
	(0.99–1.32)	(0.99–1.32)	(1.01–1.35)	(1.05–1.42)
Quintile 3	0.98	0.98	0.98	1.03
	(0.84–1.13)	(0.85–1.14)	(0.84–1.14)	(0.88–1.20)
Quintile 4	1.14	1.14	1.18*	1.25**
	(1.00–1.31)	(1.00–1.31)	(1.03–1.36)	(1.08–1.44)
Quintile 5	1.27***	1.25***	1.29***	1.33***
	(1.12–1.44)	(1.10–1.42)	(1.13–1.48)	(1.16–1.53)
Education (ref = mandatory)				
Secondary school		0.97	0.95	0.92
		(0.88–1.08)	(0.85–1.05)	(0.83–1.02)
Higher education		1.06	1.08	1.09
		(0.94–1.20)	(0.95–1.21)	(0.96–1.23)

CI: confidence interval; HR: hazard ratio; ref : reference group. Disposable income was divided into quintiles, where quintile 1 represents the most disadvantaged and quintile 5 the most advantaged. Model 1: Crude HR of disposable income; Model 2: HRs adjusted for education; Model 3: Model 2 + demographic variables (age, sex, year of first dialysis, marital status, citizenship, and home county); Model 4: Model 3 + clinical variables including blood type, primary renal disease, and comorbidities. ***p<0.001; **p<0.01; *p<0.05.

Table 6: Association between education and access to the waitlist and kidney transplantation conditional on waitlist placement, by Cox proportional hazard regression

Variables included in the model	Model 1: Crude HR of education (95% CI)	Model 2: Adjusted for demographic variables, HR (95% CI)	Model 3: Adjusted for Model 2 + clinical variables, HR (95% CI)
Access to the waitlist (n=13,982)			
Education (ref = mandatory)			
Secondary school	2.11*** (1.93–2.31)	1.38*** (1.26–1.51)	1.35*** (1.23–1.48)
Higher education	3.32*** (2.99–3.68)	2.37*** (2.13–2.63)	2.16*** (1.94–2.40)
Access to kidney transplantation conditional on waitlist placement (n=2,694)			
Education (ref = mandatory)			
Secondary school	0.99 (0.90–1.09)	0.97 (0.88–1.08)	0.95 (0.86–1.05)
Higher education	1.12 (1.00–1.25)	1.14* (1.02–1.28)	1.16* (1.03–1.30)

CI: confidence interval; HR: hazard ratio; ref: reference group; Model 1: Crude HR of education; Model 2: HRs adjusted for demographic variables (age, sex, year of first dialysis, marital status, citizenship, and home county); Model 3: Model 2 + clinical variables including blood type, primary renal disease, and comorbidities. ***p<0.001; **p<0.01; *p<0.05.

Paper III

Treatment effect of kidney transplantation on survival time compared with dialysis

In Paper III, we quantified the survival time of KTx relative to dialysis using the advanced propensity score weighting approach for patients on the waitlist. The model assessments showed that both the treatment model and outcome model were suitably specified, and the overlap plot confirmed that the overlap assumption was not violated. After weighting, the baseline covariates were balanced between the KTx and dialysis groups. The estimated survival time would be 23 years if all the patients received KTx, almost 14 years longer than if all the patients received dialysis (Table 7). A subgroup analysis by sex revealed that the ATE was larger for men than for women, but the difference was not significant (p=0.90; Table 7).

When not limited on the waitlist, the average survival time was estimated to be around 16 years if all RRT patients received KTx, which was about 11 years longer than if all RRT patients received dialysis. For either men or women, the ATEs were similar to each other and no ATE difference existed between men and women (p=0.86). Analysis of the subsample from Region Skåne and Stockholm County Council revealed that the estimated survival times were similar for both KTx and dialysis regardless of whether the Charlson comorbidity index was included or not, confirming the stability of our results in the main analysis for the whole of Sweden.

Table 7: Average treatment effect of treatment on survival time for patients on the waitlist and subgroup analysis by sex (n=2,676)

	Coef.	p	95% CI	
ATE				
KTx vs. dialysis	13.79	0.000	11.37	16.21
POM				
KTx	23.08	0.000	21.16	25.01
Dialysis	9.29	0.000	7.77	10.81
Subgroup analysis by sex				
ATE: men				
KTx vs. dialysis	14.44	0.000	11.25	17.62
POM: men				
KTx	22.88	0.000	20.82	24.95
Dialysis	8.45	0.000	6.61	10.28
ATE: women				
KTx vs. dialysis	13.86	0.000	6.17	21.54
POM: women				
KTx	24.24	0.000	19.01	29.47
Dialysis	10.38	0.006	2.97	17.80
Test ATE: –women + men = 0				
(1)	0.58	0.896	-8.13	9.30

CI: confidence interval; KTx: kidney transplantation; ATE: average treatment effect; POM: potential outcome mean.

Paper IV

Treatment effect of kidney transplantation on healthcare costs compared with dialysis

When estimating healthcare costs after KTx for waitlisted patients in Paper IV, we estimated the total healthcare costs after KTx up to the third year and the total healthcare costs over three years after KTx, and then separately estimated inpatient costs, and outpatient and primary care costs after KTx up to the third year.

Table 8 shows the estimated POM and ATE on total healthcare costs for waitlisted patients. The estimated total healthcare costs in the first year after KTx (including the KTx surgery costs) assuming all patients received KTx were around €64,000, which was €21,842 higher than under the assumption that all patients received dialysis (€42,155). However, the estimated total costs for the second and third years were €39,004 and €57,428 lower, respectively, if all patients received KTx rather than if all patients received dialysis. The ATEs were estimated to be €97,790 and €113,891 higher from dialysis compared with KTx over three years and over lifetime after KTx, respectively. In the first year after KTx, the estimated average inpatient cost would be €46,297 if all patients received KTx which was €22,324 higher than if all patients received dialysis. The estimated outpatient and primary care costs would be €11,887, €27,017, and €42,392 lower if all patients received

KTx rather than all patients received dialysis for the first, second, and third year, respectively, after KTx.

Table 8: Average treatment effect of treatment on healthcare costs (€)

	Coef.	p	95% CI	
First year after KTx (n=739)				
ATE				
KTx vs. dialysis	21,842.4	0.006	6,159.8	37,525.0
POM				
KTx	63,998.0	0.000	52,646.9	75,349.0
Dialysis	42,155.6	0.000	32,473.6	51,837.5
Second year after KTx (n=582)				
ATE				
KTx vs. dialysis	-39,004.4	0.000	-60,727.5	-17,281.4
POM				
KTx	12,701.0	0.000	6,967.1	18,435.0
Dialysis	51,705.4	0.000	31,557.3	71,853.6
Third year after KTx (n=499)				
ATE				
KTx vs. dialysis	-57,427.8	0.001	-91,148.6	-23,706.9
POM				
KTx	11,074.0	0.000	5,665.0	16,482.9
Dialysis	68,501.7	0.000	33,949.5	103,054
Total costs over three years after KTx (n=480)				
ATE				
KTx vs. dialysis	-97,789.6	0.002	-160,146.4	-35,432.8
POM				
KTx	79,819.0	0.000	63,870.3	95,767.6
Dialysis	177,608.5	0.000	122,086.6	233,130.5
Overall costs over life years after KTx (n=873)				
ATE				
KTx vs. dialysis	-113,891	0.000	-177,756.2	-50,025.0
POM				
KTx	129,040.5	0.000	108,019.9	150,061
Dialysis	242,931	0.000	183,398.3	302,463.8

CI: confidence interval; KTx: kidney transplantation; ATE: average treatment effect; POM: potential outcome mean. €1=SEK8.7053

Discussion

Main findings

This thesis includes four papers which together explore the SES-related health inequalities in access to the process of KTx as well as comparing prognosis outcomes such as survival time and healthcare costs of KTx relative to dialysis.

The results show a strong association between SES and access to KTx in general (Paper I). In the multivariate analysis, patients in the highest income quintile had a more than three times greater chance of receiving KTx compared with patients in the most disadvantaged quintile. An equally large effect was found for patients with higher education compared to patients with mandatory education alone.

After separating the process into access to waitlist and access to KTx conditional on waitlist placement (Paper II), patients in the highest income group had a more than 1.7 times and 1.3 times increased chance of access to the waitlist and KTx, respectively, compared with patients in the lowest income group. Patients with higher education had more than 2 times and 1.16 times higher chance of access to the waitlist and KTx, respectively, compared with patients with only mandatory education.

We assessed the POM and ATE for survival time of KTx relative to dialysis using the double-robust IPWRA approach for patients on the waitlist (Paper III). KTx increased survival time significantly, with a survival advantage of almost 14 years compared to dialysis. Although men's estimated average survival advantage was about 0.5 years longer than women's, this difference was not statistically significant.

We also estimated the POM and ATE for healthcare costs of kidney transplantation relative to dialysis, using the same method as above to control for selection bias (Paper IV). KTx was associated with higher total healthcare costs than dialysis in the first year after KTx, but lower total healthcare costs in the second and third years. Over the three years and over lifetime after KTx, KTx was healthcare-cost-saving in relation to dialysis. For inpatient costs, KTx also had higher costs than dialysis in the first year after KTx, while for outpatient and primary care costs, KTx had lower costs than dialysis in each of the first three years after KTx.

Main findings in relation to other research

The findings in this thesis are generally in line with the findings from previous studies suggesting that higher SES is associated with a higher chance of access to the KTx process [16-18, 44, 78]. For example, Schold et al. [17] found that higher income was associated with increased likelihood of receiving a transplant, which was consistent with our results which did not separate living- and deceased donor kidney transplantation. Schaeffner et al. [16] found that more highly educated patients had greater likelihood of access to KTx in the USA, which again was consistent with our results. Regarding access to waitlist and KTx conditional on waitlist placement, studies from the USA have shown an association between living in lower-SES neighborhoods and decreased likelihood of completing the steps to KTx [17, 78]. Studies from the USA have also shown that higher education was associated with a greater likelihood of being placed on the waitlist and undergoing KTx [16, 18]. However, there are a few studies reporting contrary findings. The International Dialysis Outcomes and Practice Patterns Study (DOPPS) found that when controlling for both income and education, income was highly positively associated with access to KTx but education was not [27]. This difference may be because DOPPS included patients from several countries, and education systems and even the meanings of educational levels may differ between countries [16]. In addition, the patients in the DOPPS study were aged 18–65 years old whereas our studies included adult patients of all ages. However, our sensitivity analysis for working-age patients (18–65 years) still showed a strong positive association between education and access to KTx. Axelrod et al. [44] found that socioeconomic advantage (mainly using postcodes as SES indicator) was highly positively associated with both living and deceased donor KTx, while Grace et al. [23] found that socioeconomic advantage (using postcodes as SES indicator) was only highly positively associated with living donor KTx, not with deceased donor KTx. When we also separated KTx into living and deceased donor transplantation, our results were consistent with the study by Axelrod et al [44]. Studies from France [22] and the United Kingdom [19] found no effect of neighbourhood SES on likelihood of being waitlisted or receiving KTx. In our study (Paper II), although the effect size of SES was lower for getting a transplant compared with being placed on the waitlist, it was still significant. These conflicting results between our studies and prior studies may be due to using individual-level rather than area-level measures of SES (e.g., neighborhood deprivation, degree of urbanization [22], and Carstairs score to assess social deprivation [19]). Differences in healthcare and education systems between countries might be another possible reason for these conflicting results.

Sweden has relatively strong income equity and a low degree of inequity in terms of education [79, 80]. However, we found SES-related inequalities in access to the process of KTx. There are potential explanations for this from both the patient's and

the physician's side. In Sweden, decisions regarding RRT are made by nephrologists on the basis of Swedish guidelines [81] and the corresponding European guidelines [82]. However, there are no national guidelines either for assessing eligibility for transplantation or for the allocation of kidneys. Given the lack of kidneys, physicians naturally apply various criteria to prioritize among potential recipients as a means of rationing this limited resource. The possibility of physician bias thus cannot be ruled out in identifying potential transplant candidates; and, moreover, is difficult to capture [83, 84].

From the aspect of the patients, there are several possible sources of inequalities. Firstly, higher-SES patients might find it easier to overcome the communication barriers between patients and healthcare providers [16]. The results of our sensitivity analysis provide some support for this theory, as the effect size between income and education and access to pre-emptive transplantation (where human decision plays a great role) was substantially higher than that between income and education and later KTx. The sensitivity analysis thus also reflected the potential physician bias. Secondly, lower-SES patients may have more, and more severe, comorbidities and worse adherence compared with higher-SES patients, because there is a known association between SES and medication and health advice compliance [16, 85, 86]. Though we controlled for comorbidities in our studies, information on the severity of comorbidities was not available. Thirdly, higher-SES patients may actively seek living donors while lower-SES patients may be hindered in this due to a lack of awareness or means [24]. In addition, lower education is associated with factors such as smoking, less exercise, and being overweight, which are either relative contraindications to transplantation in themselves or factors with an impact on comorbidities that are contraindications [87]. Differences in knowledge, attitudes to disease and treatment, and preference for transplantation may lead to different treatment choices by SES-disadvantaged patients compared to SES-advantaged patients [19]. However, we did not control for these factors due to lack of the relevant information. Health inequalities can be defined as differences in health status or in the distribution of health determinants between different population groups; for example, differences in mobility between elderly people and younger populations or differences in mortality rates between people from different social classes [88]. It is important to distinguish between inequality in health and inequity. Some health inequalities are attributable to biological variations or free choice, and others are attributable to the external environment and conditions mainly outside the control of the individuals concerned. In the first case, it may be impossible or ethically or ideologically unacceptable to change the health determinants, and so the health inequalities are unavoidable. In the second, the uneven distribution may be unnecessary and avoidable as well as unjust and unfair, so that the resulting health inequalities also lead to inequity in health [88]. Hence, SES may have both a direct effect on access to the KTx process (e.g., through

discrimination) and an indirect effect (operating through patients' preferences) [89]. The SES inequalities found in this thesis are therefore not necessarily due to discrimination. However, they will still contribute to societal inequalities in health and wealth, and as such, it is of interest to mitigate them.

The effect size of inequalities in access to the waitlist was larger than that on access to KTx once on the waitlist. The decision to put a patient on the waitlist is probably more subjective and more vulnerable to inequality, because this entails a closer relationship between the treating physician and the patient. The transplantation decision once on the waitlist is more objectively based on medical factors without the patient necessarily meeting the transplantation surgeon.

We also found that the association between education and waitlist access was stronger than the association between income and waitlist access. Due to the more subjective decision to waitlist compared with KTx, this could be explained by education potentially capturing other aspects such as knowledge and attitudes to disease and treatment, compliance, and/or communication skills. Education could therefore be expected to be more related to the likelihood of being waitlisted compared to income. In addition, on one hand, income could be more affected due to the disease and therefore a "poorer" measurement of SES; but on the other hand, income should be less important in a public tax-funded system.

Previous studies have usually used the (relative) hazard ratio as the effect measure when comparing mortality between different treatments, and so comparing our results directly to prior studies is not feasible. However, our findings confirm the previously-reported survival advantage of KTx [9, 31, 36]. Moreover, this thesis provides information on the length of the survival advantage in absolute terms, which is important for several reasons; for example, it can be used in economic evaluations of interventions. Unlike previous studies, our work took account of both the selection bias to different treatment modalities and the selection bias related to waitlist, and applied advanced statistical analyses comparing KTx with dialysis. Bayat et al. [36] compared the survival of KTx patients with that of general dialysis patients in a French region, focusing on elderly patients. Using an estimated propensity score to control for non-random treatment assignment to the waitlist for KTx, they showed that KTx produced longer survival. However, the mortality of general dialysis patients was higher than that of dialysis patients on the waitlist, because of selection into waitlist [36]. Our study compared KTx patients with waitlisted dialysis patients and used the propensity score weighting method, which to some extent reduces the second selection bias. We also compared KTx patients with general dialysis patients and found that general dialysis patients had shorter survival than KTx patients, which is consistent with the study of Bayat et al. [36]. In the subgroup analysis, women had longer survival time than men in both KTx and dialysis therapy, both for patients on the waitlist and for all RRT patients. The

higher POM for women might reflect their longer life expectancy in general. However, there was no statistically significant difference in ATE between men and women. As seen in Paper II, women have the same chance as men to access KTx, and so it seems that there is no sex inequality either in access to KTx or in survival advantage of KTx.

Regarding the treatment effect on total healthcare cost, we found that KTx incurred a higher cost than dialysis, most likely mainly due to the high cost of the transplantation surgery. However, we did not include the cost of immunosuppressive and other drugs, which may have led to an underestimation of the KTx cost. Regarding the inpatient care cost, we noticed that in many cases this cost was zero from the second year after KTx. There are several possible reasons for this. For example, one possibility is that the patients were in good health following their transplant surgery, while another is that the patients moved out of the studying regions, and there were no registers of their inpatient care utilization during the certain study period. For outpatient and primary care costs, we found that KTx also had lower cost in the first year, showing that the majority of the first-year cost of KTx occurs via inpatient care. However, previous study found that outpatient care cost accounted for 71% of the mean annual cost for dialysis [90].

We also combined the results from Papers III and IV to conduct a simple economic evaluation between KTx and dialysis. In Paper III, we estimated that the survival advantage of KTx compared with dialysis was 13.79 years. In Paper IV, we estimated the treatment effect on healthcare costs of KTx compared with dialysis, and found that KTx was cost-saving by €113,891 compared with dialysis. The results from this two studies show that KTx is a better and cheaper treatment. Another study using the same patients found that KTx was superior to dialysis in terms of labor market outcomes such as the potential to return to work and risk of early retirement [91]. KTx dominates dialysis in these three aspects at least.

Strengths and limitations

The major strength of this thesis is the use of several registries to provide extensive and detailed information. The SRR covers almost all RRT patients in Sweden and has 95% data reporting incidence. The individual-level SES indicators from LISA database, income and education, better capture SES and thereby give more accurate effect estimations than area-level SES. Data from several national registries give the studies high power and excellent generalizability within the Swedish setting. The extent of the information ensures that as many confounding factors as possible can be adjusted for in order to minimize systematic errors. Our data enable the taking

into account of a large set of demographic and socioeconomic factors, all major primary renal diseases, and comorbidities; this is in contrast to previous studies.

Another advantage of this thesis is the use of advanced propensity score weighting to deal with the treatment selection bias. Propensity score methods are often applied incorrectly when estimating the effect of treatment on time-to-event outcome. Common errors include the use of inappropriate statistical tests and the failure to correctly assess if the specified propensity score model has induced an acceptable balance in baseline covariates between treatment and control groups [66]. Unlike previous studies, we did not only test the assumptions when using the propensity score method, but also checked baseline balance after weighting and model assessments to confirm the double-robust property of IPWRA, which increases the credibility of our results. Although the hazard ratio is a popular effect measure when comparing the mortalities of different treatments, it is mainly useful when the treatment enters linearly and the distribution of the outcome has a proportional-hazards form [92]. However, when using the ATE as an effect measure, neither linearity in treatment nor proportional-hazards form is required. Moreover, the ATE measures the effect in the same time units as the outcome instead of in relative conditional probabilities, and is also much easier to explain even to non-technical audiences [93].

In addition to the strengths above, some limitations should also be noted. The register data do not include biochemical data (e.g., serum albumin level, levels of parathyroid hormone) which are known factors influencing access to KTx. However, these biochemical covariates are unlikely to be correlated with SES [94]. Additionally, we had information on comorbidities but not about their severity, nor about changes during follow-up.

Although we controlled for observable variables to reduce selection bias when estimating the treatment effects, unobservable variables may still have influenced the results. However, unobservable variables are only a problem if they are correlated with both treatment selection and outcome measure. If this is the case but the unobservable variable is highly correlated with controlled observable variables, the results with respect to treatment effects should not be much affected. Still, if an unobservable variable is not correlated with any controlled observable variables, the results may be influenced. Nevertheless, the linked database provided a very rich source of information, and we made extensive use of the information available in it in order to minimize this risk.

Generalizability

It is important to consider the generalizability and external validity of the findings in this thesis. The findings from Papers I–III are based on national observational register data covering almost all RRT patients in Sweden, which should ensure a high level of generalizability within the Swedish setting. Although the healthcare cost findings from Paper IV are based on the observational data from just two healthcare administrative areas (Region Skåne and Stockholm County Council, which together cover around a third of the Swedish population), due to the standardized treatments and similar assignment of treatments we also think these results can be generalized to other regions in Sweden. However, regarding the external validity, the extent to which the findings may be extended to other countries is unclear. Firstly, the finding from this thesis may not be generalizable outside the Swedish health care system and education system. Sweden is a high-income country with a publicly-funded universal healthcare system, free access to higher education system, and no waitlist for ESRD care except for KTx. In other countries, especially low and middle income countries, the SES-related health inequalities in access to the KTx process are likely larger than that in Sweden. Secondly, even if the procedures of treatments for ESRD are similar in different countries, the post-treatment nursing care may be different. The absolute survival time in our study thus may not be applicable to other counties. However, the relative estimation may be used in other contexts. Thirdly, different countries have different pricing systems, which may limit the generalizability of our findings regarding the healthcare costs after KTx.

As all Nordic countries have fairly similar tax-funded healthcare and education systems, the generalizability of our findings in Sweden should be high, at least for the findings regarding SES-related inequalities and survival time.

Policy implications

The findings from this thesis provide the basis for several policy implications. Firstly, the findings show that lower-SES patients have a reduced chance of access to KTx. As discussed above, the SES inequalities are not necessarily due to discrimination. Some inequalities are attributable to biological variations or free choice and other are attributable to external environment and conditions mainly outside the control of the individual's concerned. If the effect of SES is manifested via such as patients' biological variations, it may be impossible to avoidable. If the effect of SES is through patients' preference (e.g., lower SES patients smoke more), we should do something to mitigate them while if the effect of SES is through other

patients' preference, it may be ethically or ideologically unacceptable to change and the inequalities are unavoidable. However, if the effect of SES is through discrimination, then mitigation is necessary, and in this case policies should assist vulnerable patients. Secondly, the results suggest that KTx dominates dialysis in terms of both survival time and healthcare costs. Even though KTx has been recommended and should be more actively recommended, expansion of KTx is hampered by lack of donor organs, and so strategies to improve the availability of organs for transplant could have major health and economic implications. For example, we can perform some education programs to encourage people donating organs or introduce relevant knowledge to reassure donor's worries about donation.

Future research

The findings from this thesis have revealed SES-related health inequalities in access to the process of KTx. However, the mechanisms behind the observed SES inequalities are unknown. Understanding the reasons for these apparent inequalities is important if the aim of the health care system is to provide good and equal healthcare for all citizens. Further research is therefore needed to explore the potential mechanisms behind these inequalities, in order to assess whether the inequalities are unfair, and if so to construct interventions to reduce SES-related barriers.

This thesis has estimated comparable prognosis outcomes including survival time and healthcare costs of KTx and dialysis, which can provide evidence for economic evaluations of programs aimed at increasing the kidney supply. Further studies are also needed to estimate quality of life following both KTx and dialysis. Cost-utility analysis can thus be performed by combining the costs and quality of life studies. In addition, if data are available, it would also be interesting to explore whether there are SES-related inequalities in prognosis outcomes.

Due to limited sample size, we only estimated healthcare costs up to the third year after KTx, and so further studies are needed to compare healthcare costs between KTx and dialysis over a longer follow-up period. There is also a need for comparable studies of KTx and dialysis that include more cost items, such as indirect costs, direct non-medical costs, and medication costs. The inclusion of these items may change the average treatment effects dramatically; medication costs may play a major role in KTx after surgery, while indirect costs may play a major role in dialysis. A previous study from Sweden found that prescription drugs constituted almost 50% of the mean annual cost of €15,500 for KTx patients [90]. Considering the different cost items will give us a comprehensive understanding of RRT and a relatively accurate comparison between KTx and dialysis.

Conclusions

The findings in this thesis show that patients with higher income and education have higher chance of KTx in general, access to the waitlist, and access to KTx conditional on waitlist placement. KTx is associated with a longer survival time and lower healthcare costs than dialysis. The main conclusions that can be drawn from this thesis are:

- There are SES-related inequalities in access to KTx in general among ESRD patients.

- There are also SES-related inequalities in both access to the waitlist and access to KTx conditional on waitlist placement. Moreover, the former inequalities are substantially larger, and can therefore be expected to contribute more to societal inequalities.

- KTx has a survival benefit of almost 14 years relative to dialysis among Swedish ESRD patients with RRT. Thus, KTx should be more actively recommended in Swedish populations.

- KTx is healthcare-cost-saving in the long run.

- KTx is cost-effective, and dominates dialysis.

- SES-advantaged patients have longer survival times than SES-disadvantaged patients.

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