European disparities in the incidence and outcomes of children with end-stage renal disease
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General Discussion
GENERAL DISCUSSION

In this thesis, we aimed to reveal health inequalities and provide information to improve outcomes in the European paediatric RRT population. In this chapter, we will discuss the main findings and their implications for health policy and clinical practice.

MAIN RESULTS

- Considerable disparities exist in RRT incidence rates and mortality risk between European countries. The lowest incidence rates and highest mortality risk were found in several Eastern and Central European countries, whereas the opposite was evident in most Western and Northern European countries.
- Country differences regarding the genetic susceptibility to certain renal diseases played only a marginal role in explaining the differences in RRT incidence and survival between countries.
- Disparities in RRT incidence and mortality risk between countries were largely explained by differences in country macroeconomics, which limit the availability and quality of paediatric renal care in countries burdened under financial constraints, especially in the youngest children.
- Children selected to start on HD had an increased mortality risk compared with those on PD, especially during the first year of dialysis, and when seen by a nephrologist for a shorter time prior to dialysis. This treatment effect was less pronounced in patients under 5 years of age at dialysis initiation and in the infant dialysis population.
- Grafts from older living donors provided excellent graft survival across all recipient age groups.
- The youngest deceased donors showed the poorest graft survival in the youngest recipients, whereas deceased donor age had little effect on graft failure in adolescent recipients.
European disparities in the paediatric RRT population

As defined by the WHO, the term ‘health disparity’ may best be described as “the unfair and avoidable differences in health status seen within and between countries”, and has been recognized as a key area for improvement by all WHO member states [238]. Correspondingly, two of the main aims of the European health policy framework (Health 2020) are to 1) significantly reduce health inequalities and 2) ensure health systems that are universal, equitable, and of high quality [14]. While the concept of health disparities may be viewed from various angles, such as race, gender, or socioeconomic status, in this thesis we focus on geographical health disparities. The first step necessary to achieve equitable health across Europe is to measure the magnitude of existing disparity.

We reveal considerable disparities in the provision and quality of paediatric renal care across Europe. RRT incidence varied from 0.0 cases per million children (pmc) in Malta to 9.8 pmc in the UK (IQR 1.8-7.7), and mortality rates varied from 0.0 deaths per 1000 patient years in Iceland to 81.9 in Bosnia and Herzegovina (IQR 6.5-16.1). Although random variation may partly explain these differences, especially due to the inclusion of several smaller countries with a limited number of patients, a clear geographical pattern was evident. Compared to Western, Northern, and Southern European regions, where the RRT incidence rate was between 7-8 cases pmc, the Eastern European region treats a relatively low number of children, with an incidence rate of 3.6 pmc. Similarly, most of the variation we demonstrate in country mortality rates across Europe was attributable to an excess mortality risk in several Eastern European countries, whereas mortality risk was mostly similar in patients treated in other regions. Having defined the inequities in chapters 3 and 4, the next step in achieving equitable health was to explore potential factors explaining these disparities.

Disease distribution explains little of the variation in country RRT incidence and mortality rates

Variation in rates of paediatric RRT across Europe may be caused by geographical differences in disease occurrence. This has been previously demonstrated in the adult RRT population, where differences in the occurrence of diabetes and hypertension in the general population, the two main causes of ESRD in adults, explained 79% of the variation in incidence between Germany, England, and Wales [239]. In addition, national studies in France and Denmark
associated regional variation in incidence of RRT in adults with the prevalence of diabetes [240, 241]. Globally, the EVEREST study found an association between general population diabetes prevalence and RRT incidence for diabetic ESRD, although surprisingly this was not the case for overall RRT incidence [19]. Furthermore, as chronic kidney disease has a genetic component, country variation in adult RRT incidence has also been linked to genetic variation [242, 243].

In children, international differences in the disease occurrence of rare disorders with a genetic component, such as childhood cancers, have been linked to geographical variations in genetic susceptibility [244, 245]. As nearly all cases of paediatric onset ESRD consist of rare disorders with at least some genetic origin, differences in treatment rates across Europe could be explained by geographical differences in disease occurrence. However, in chapter 3, we demonstrate that relative differences in disease distribution only play a marginal role in explaining the variation in RRT incidence across European regions. A notable exception was the higher incidence of hereditary nephropathies in Northern Europe, which was likely due to the higher incidence of Finnish type nephropathy common in Scandinavian countries, and explained 8% of the higher RRT incidence found in Northern Europe relative to the rest of Europe.

Although the relative distribution of renal disease was similar across Europe, country differences in the ability to successfully treat various diseases may still contribute to variation in country mortality risk. However, in chapter 4, we demonstrate that this factor only increased the variation in mortality risk between countries by 8%, suggesting that countries are more or less equally capable of treating varying renal diseases. In line with our results, Hölttä et al. demonstrated that patients suffering from congenital nephrotic syndrome of the Finnish type treated in Finland, where nephrologists have ample experience in treating this disease, had similar survival probabilities compared to RRT patients with Finnish type treated in other European countries [246]. Subsequently, having eliminated relative differences in disease occurrence as a major cause for geographical variation in incidence and mortality risk, we then focused on country-level factors affecting access-to-care and quality of care.
Discussion

Macroeconomics

It has been well established that economic welfare is an important determinant of population health and access to health services. Health care expenditure is determined by the volume and cost of health care in a country, with wealthier countries tending to spend more on health care [247]. Health care expenses have grown steadily over the past decades, driven primarily by medical advances in technology [248, 249], and correlate well with health spending on ESRD patients [250, 251]. In the adult RRT population, the EVEREST study demonstrated that a higher country wealth and health care expenditure were associated with a higher RRT incidence [19]. Similarly, Schaefer et al. previously demonstrated that country mortality rates in were strongly affected by gross national income in countries across the globe in the paediatric PD population [23], and Harambat et al. revealed that disparities in transplantation rates across Europe were related to economic differences [42].

In the European paediatric RRT population, we found higher treatment rates in wealthier countries, which tend to spend more on health care and where patients bear less out-of-pocket health expenditures. The association between these macroeconomic indicators and the provision of care is understandable given the complexity and cost involved in the provision of renal care to children by a multi-professional paediatric team in an academic setting. Furthermore, in countries with limited funds available for health care spending, the health agenda may prioritize resources towards the more dominant high-burden diseases, thus allocating less funds towards the expensive treatment of rare diseases [81]. Nonetheless, these results indicate that the need for paediatric RRT is not being met by governments burdened under financial constraints, and is a cause for concern, as non-acceptance to RRT implies mortality. Encouragingly, we identified a ceiling effect in countries spending >7.5% of GDP on healthcare, suggesting that RRT for all children with ESRD is attainable with healthcare spending around this margin. A similar ceiling effect was identified by a WHO study in the adult RRT population, where country wealth above a GDP per capita of $20 000 per year had little effect on RRT incidence [25].

Similarly, the majority of variation in country mortality rates across Europe was explained by differences in country public health financing, with restricted public health expenditure adversely affecting mortality risk in our population. Importantly, this implies that in countries
with limited spending on health services, children in need of RRT are not only dying due to limited access to treatment, but also as a result of substandard care. Interestingly, the opposite was found in the adult dialysis population, where greater country wealth was associated with an increased mortality risk, likely reflecting the acceptance of older and more frail patients in countries with sufficient resources [20]. This implies that the allocation of health care funds to paediatric RRT, and a subsequent higher acceptance of younger high-risk patients, is more effective in terms of patient survival compared to more financial resources allocated to high-risk patients in adult RRT.

The youngest patients
Despite the substantial improvements made over the past decades regarding treatment of the youngest patients [34, 68], the provision of RRT to these patients remains technically challenging due to small body size, higher risk of infection, difficulties in nutrition and growth, and a high incidence of severe comorbidities [116, 117]. Although the improvements in survival over the past decades have been the greatest in these young patients, mortality risk remains the highest of all paediatric patient age groups. We show that the disparities regarding both country RRT incidence rates and mortality risk were particularly evident in this age category. Importantly, we demonstrate that differences in country macroeconomics disproportionately affect access to treatment for the youngest patients, finding that wealthier countries, spending more on health care, were accepting patients for treatment at a younger age. This was not unexpected given that the youngest patients are the most complex and costly to treat, but implies that poorer European countries are lacking the capacity to treat these vulnerable patients [12].

Counterintuitively, we also found the highest survival rates in countries spending the most on health care, despite the higher acceptance of complex young patients whom bear the highest mortality risk. Vice versa, in countries burdened under financial constraints, where access-to-care was limited for the youngest patients, we found the worst survival rates. As non-acceptance to RRT implies an underestimation of ESRD mortality, the disparities in mortality caused by differences in country macroeconomics are amplified in countries with limited resources. Furthermore, initially contradicting our hypothesis, we found no association between country GDP per capita and mortality on RRT. However, after adjustment for patient
age distribution as a mediator, an inverse relationship became statistically significant, suggesting that, in countries with limited resources, the lower acceptance of young, high-risk, patients was masking the inverse association between GDP per capita and mortality.

As an expected unacceptable quality of life forms an important factor in the decision to withhold or withdraw treatment [117–120], country differences in the physicians’ willingness to treat the youngest patients at the limit of viability may also play a role in explaining the variation in incidence rates [252]. Indeed, the acceptance of these patients is not self-evident, as a recent survey indicated that 70% of paediatric nephrologists sometimes refuse RRT to children under 1 month of age, and 50% to children between 1-12 months of age [205]. As this survey was conducted in affluent countries (Canada, Germany, United States, Japan, and the UK), one may speculate that countries with limited (financial) capacity may further pre-dispose physicians towards an even higher non-acceptance of these complex and costly patients, compared to the wealthier countries included in the survey.

Country indicators of access to care and quality of care

Although we found clear associations between macroeconomic indicators and the provision and outcomes of paediatric RRT, the exact mechanisms explaining these relationships remain unclear. In adults, factors such as the availability of renal services, timing of dialysis initiation, travel time to dialysis facilities, and renal service organizational indicators all play a role in explaining the variation of RRT incidence [18, 19, 25, 239, 253–255]. Therefore, we studied the relationship between other country indicators of access to care and quality of care, hoping to find actionable indicators and evidence that may explain the causal pathway downstream from macroeconomics.

We studied the effect of physical access-to-care indicators on RRT incidence, finding higher incidence rates in more urbanized countries and in countries with a high paediatric population density, suggesting that health services are physically more accessible in countries where patients may expect shorter average travel times and lower costs compared with more rural countries with a low paediatric population density. Similarly, in the UK, on a regional level of analysis, it has been shown that adults who live in (rural) areas that are further from a dialysis unit, have a lower chance of starting RRT [18, 256]. Conversely, we found no association with
the density of paediatric RRT centres and RRT incidence. This may be explained by the improved availability of paediatric renal care throughout Europe over the past years [68]. In 1998, 90% of European countries were able to provide paediatric dialysis and 55% paediatric transplantation, with only 30% of Eastern European countries able to provide the latter [81]. In our current survey, all European countries were able to provide at least one modality of paediatric dialysis, which may explain the lack of association between the density of RRT centres and incidence rates.

We studied the effect of country child mortality rates, as a proxy for the effectiveness and accessibility of paediatric health services in general. We found an inverse trend between neonatal mortality and RRT incidence in the youngest patients, independent of country wealth, suggesting that the effectiveness of a country’s paediatric health care system is associated with access to RRT in the youngest patients. Moreover, a countries’ neonatal mortality rate was inversely associated with mortality on RRT and explained a large portion of the variation in country RRT mortality risk, reflecting the impact of the quality of paediatric health systems on the effectiveness of paediatric RRT care. However, the association between neonatal mortality and both RRT incidence and mortality was attenuated after adjustment for macroeconomic indicators, reflecting how the quality and accessibility of paediatric renal care services are – to some extent – reliant on country wealth and public health expenditure. Similarly, we observed attenuating effects of macroeconomic indicators on the relationship between mortality risk and RRT incidence, transplantation rate, and the proportion of pre-emptive transplantations.

**Closing the East-West health gap**

We reveal that the variation in access to paediatric RRT and mortality rates was limited across Western, Northern, and Southern European countries, and mainly attributable to Eastern European countries, where patients had a significantly lower access to RRT and higher mortality risk compared to the remainder of Europe. Despite the commitments and efforts made by all European countries, our results demonstrate how disparities regarding the accessibility and quality of paediatric renal care have yet to be eliminated across Europe. Unfortunately, these results may also exemplify disparities in the quality and provision of specialized care for other complex and costly paediatric disorders across Europe. Since the fall of communism, many Eastern European countries have undergone dramatic changes in health
care infrastructure and financing, and have achieved substantial progress regarding the availability and effectiveness of renal services [81, 101, 102, 257]. While the gap between Western and Eastern Europe has narrowed progressively over the past decades, many countries in Eastern Europe remain burdened under limited health care budgets, with public health care expenditure ranging from 2-3% (as a percentage of GDP) in the lowest ranking countries of Europe (Albania, Cyprus, Ukraine, Montenegro, and Russia), to 9-10% in the highest ranking countries (Sweden, The Netherlands, Denmark, France, and Austria) [75]. Financial support may be available through the EU cohesion policy, which primarily aims to reduce social and economic disparities across Europe through project investments by various EU funding bodies. Investments in health care infrastructure may help reduce these disparities, although only countries with a GDP < 90% of the EU27 average are eligible. Furthermore, after their accession to the EU, many Eastern and Central European countries experienced ‘brain drain’; an outflow of health professionals to higher-income countries [103–105]. This may potentially cause larger problems in the future, given the inverse association found between RRT mortality and the number of paediatric nephrologists working in a country per million children.

In efforts to close the East-West health gap, national and European policy-makers have pursued a uniform and high quality level of care for the prevention and treatment of rare diseases across Europe. However, to date, evidence has been lacking regarding European disparities specific to the field of paediatric onset ESRD. By revealing the magnitude of health-care inequalities across Europe, we hope to increase the awareness in the paediatric nephrology community and amongst policy makers on the European, national, and regional levels, and provide the necessary evidence required to advocate policy change and inform budgetary decisions on various levels of government. Currently, within various national and European policy frameworks, many countries have adopted national strategic plans to improve (the organization of) care for patients suffering from rare diseases. However, considering the austerity-driven cuts in healthcare budgets experienced by most European countries over the past few years as a result of the financial crisis, implementing these plans poses a challenge for health care policy makers, and many plans have limited funding or no funding at all [258]. In further consolidation efforts, over the past years, the European Committee of Experts on Rare Disease has been instrumental in establishing Centres of Expertise for Rare Diseases.
These centres have been successful in improving the quality of care for these patients, however, the organization of centres currently varies considerably between countries. Linking existing centres of expertise throughout Europe via the European Reference Networks should help facilitate the sharing of expertise on rare diseases between European health providers, and expand the opportunities for cross-border diagnostics and treatment [259]. From a clinical perspective, we advocate further standardization of treatment guidelines and medical training for paediatric nephrologists across Europe. Examples include recommendations for the training of paediatric nephrologists (formulated by the European Society for Paediatric Nephrology), information exchange through international fellowships, and the provision of Continuing Medical Education courses across Europe [106].

The bigger picture
Internationally, RRT incidence rates in other developed countries with a publicly funded paediatric RRT programme (and thus ‘universal access’ to treatment), such as Japan and Malaysia and Australia and New Zealand, are similar to the average European RRT incidence of 5.4 per million children. The USA forms an exception, where the incidence rate is approximately double that of Europe, potentially as a result of differences in race and SES, and an earlier start on RRT [61–63]. In developing countries however, the international disparities concerning incidence and mortality rates of paediatric RRT are far greater [168–170, 260]. Liyanage et al. estimated that in 2010, at least half of the 4.9 million people requiring RRT worldwide died prematurely because they did not have access to treatment [3]. Specifically in children, it has been suggested that possibly no more than 10% of those requiring RRT have access to treatment, and that most of these preventable deaths occurred in low- and middle-income countries [170]. The few studies available in lower-income countries, where renal registries are often lacking, confirm these disparities [171–174, 261]. Due to high cost of treatment for relatively few individuals, many developing countries prioritize resources towards improvements in health infrastructure, water and sanitation, and the prevention and treatment of high-burden (infectious) diseases. As universal access to costly RRT is unrealistic in the short term in these countries, the largest gains in survival are likely to be made by delaying progression of CKD, for example through aggressive antihypertensive treatment, and thus preventing ESRD [168, 175, 262].


**Survival on dialysis**

Despite the improvements made in paediatric renal care over the past decades, mortality in the paediatric RRT population is still between 30 and 150 times higher than that of healthy peers and occurs predominantly in the dialysis population [8, 64, 107]. Presently, the 5-year survival for paediatric RRT patients is approximately 94% across Europe. Patient survival is multifactorial, dependent on various patient and treatment characteristics, such as treatment modality. Although renal transplantation is the preferred treatment modality in terms of outcomes, approximately 80% of patients will initiate RRT on dialysis, to bridge the preparation time needed for transplantation, or will require dialysis after graft loss. Survival comparisons by dialysis modality in a randomized clinical trial (RCT) setting have proved extremely difficult. In a single RCT performed in adults, inclusion was stopped prematurely, largely due to randomization issues regarding patient preference for initial dialysis modality [147]. Consequently, survival comparisons have been reliant on observational studies. In chapter 6, we demonstrate that children selected to start dialysis on HD had an increased mortality risk compared to PD in a propensity-score matched cohort. Importantly, this risk varied by time on dialysis and in various patient sub-groups.

Consistent with several studies performed in the adult dialysis population, the mortality risk difference between HD and PD was not constant over time [151, 188, 189]. During the first 1 to 2 years on dialysis, we identified a survival advantage for paediatric patients selected to initiate dialysis on PD, after which the mortality risk became similar to those selected to start on HD. In the adult population, this initial survival advantage has previously been attributed to an improved preservation of residual renal function in PD patients [193], and forms the primary rationale for the ‘PD first’ strategy, which recommends that PD should be offered as initial modality when feasible [263]. Other potential advantages of PD in adults as initial modality include lower costs, home treatment, and a higher patient-reported quality of life [64, 264, 265].

To further explore the dialysis modality treatment effect, we stratified by time under treatment of a nephrologist prior to dialysis as a proxy for the timeliness of referral and the speed of disease progression. It is known that paediatric patients who are referred late have a poorer clinical and biochemical status and a reduced rate of pre-emptive transplantation
compared with those referred earlier [194–196], whereas the speed of renal disease progression is largely dependent on the underlying renal disease and chronic kidney disease management [65, 197]. However, to date, it was unknown whether these factors modified the effect of dialysis modality selection on mortality. We demonstrate that in patients under treatment by a nephrologist for a relatively short time prior to dialysis, those selected to start on HD had an increased mortality risk, whereas modality choice had no influence on the survival outcome in patients with sufficient time available for pre-dialysis care. This implies that in case of late referral, and when no contra-indications are present, patients should ideally be started on PD. Nonetheless, although we adjusted for some of the important confounders that may influence disease severity, such as primary renal disease and age at dialysis initiation, and excluded “crash” patients that may be limited to HD, this effect may still be the result of indication bias due to unmeasured case-mix confounders, such as the presence of severe comorbidities. Even so, improving policies and formulating interventions regarding the acceptance and preparation of dialysis are necessary to reduce the proportion of late referrals in our population.

We also identified an age-dependent treatment effect, finding that initiating dialysis on PD was beneficial in children over 5 years, but less pronounced in children under 5 years. This is supported by chapter 7, where – in sharp contrast to general belief – we demonstrate the absence of a treatment effect specifically in the infant dialysis population. Importantly, dialysis modality choice in infants was not associated with access to transplantation, suggesting that both modalities should be viewed as equally viable options. The lack of effect in younger patients may be explained by age itself, as patient age is a strong determinant of survival, the absence of treatment effect in the youngest patient may be caused by the overriding adverse effect of young patient age on mortality. Conversely, the opposite was observed in the US, where Mitsnefes et al. observed a decreased mortality risk in children younger than 5 years initiating PD compared to HD, but not in older children [34]. A different distribution of race in the USA (more blacks with a higher frequency of FSGS), and differences in clinical practice may explain this opposite effect compared to Europe. Nonetheless, in Europe, our results imply that older paediatric patients should ideally be started on PD where feasible.
Interestingly, in the wealthiest European countries, we found no significant difference in mortality risk between initial dialysis modality, whereas in the less wealthy countries, patients starting RRT on HD had a significantly worse survival compared to those starting on PD. This suggests that the majority of excess mortality found in poorer countries occurs predominantly in the HD population. This may be due to either a poorer performance on HD in these countries, or that these patients are sicker at treatment initiation and are therefore started on HD. Furthermore, given that the increased mortality on HD occurs mostly during the initial period of dialysis, early mortality is likely a main contributor to differences in country mortality risk. Similarly, in the adult population, Robinson et al demonstrated that this early, high-risk, period on haemodialysis is responsible for a great deal of the variation found in mortality between countries globally [21]. Consequently, early mortality could be an effective target for intervention to reduce mortality disparities between countries.

**Graft survival and deceased donor allocation policy**

It has been well established that renal transplantation offers better patient survival, cognitive development, quality of life, and growth compared to dialysis [8]. Fortunately, three-quarters of children with ESRD receive a transplant within 4 years after RRT initiation, however, approximately a quarter of these patients will lose their graft within 10 years after transplantation, necessitating dialysis. In chapter 8, we demonstrated how patient and donor related factors influence graft failure risk in our population. Firstly, receiving a graft from a living donor should always be preferred over that of a deceased donor, as even grafts from carefully selected older donors such as grandparents offer excellent graft survival probabilities [236, 237]. Although living donation is generally preferred above deceased donation from a clinical perspective, European countries vary the proportion of living donors, the reasons for which certainly merit further study [42]. Secondly, recipient age modifies graft failure risk, finding the poorest graft survival in the youngest and adolescent recipients. Poor graft survival in the former has been attributed to the surgical difficulties of transplantation in the smallest children, and is reflected by the increased risk during the first months post-transplantation [222, 223], and the latter due to, amongst others, poor compliance to immunosuppression regimens during adolescence [219–221]. Thirdly, in the absence of a suitable living donor, we found that the age of the deceased donor influenced graft survival, with the highest risk of graft failure in the youngest and oldest deceased donors. Lastly, we examined the impact of
Discussion
deceased donor-recipient age combinations on graft survival. We demonstrated that in the youngest recipients, those receiving the youngest donor kidneys have the higher risk of graft failure, whereas in adolescents, donor age seemed less important than adolescence itself. The deceased donor-recipient matching process is often based on a composite points-based system involving, amongst others, factors such as waiting time, HLA and blood group matching, percentage of panel-reactive antibodies, distance between donor and recipient, and medical urgency. Donor and recipient age are also often integrated in allocation schemes, and many countries have adopted a ‘young-for-young’ allocation policy. Such policies allocate paediatric donors preferentially to paediatric recipients, with the aim of reducing waiting times and providing high-quality grafts to children, but vary across Europe in their definitions of ‘young’ [42]. Due to the non-linear effects we found regarding both recipient and deceased donor age, these young-for-young polies are lacking in consistency. We therefore recommend fine-tuning these allocation schemes by increasing the granularity of the definitions of ‘young’. Specifically, in order to maximize the graft life of donor organs, we recommend prioritizing the allocation of deceased donors over the age of 11 to younger recipients and a cautionary use of small paediatric donors. In adolescents, we found poor graft survival rates across the entire deceased donor age range, precluding any specific recommendations.

METHODOLOGICAL ISSUES
Variables included in the ESPN/ERA-EDTA Registry are collected from various national sources, and therefore data may not be homogeneous. For instance, clinical measurements may be somewhat heterogeneous between countries and centres due to differing measurement techniques and laboratories. Conversely, core registry data such as patient gender, treatment modality, and various events are collected in a highly standardized manner, reducing this type of bias to a minimum. In addition, the collection of uniform data on various country renal service indicators proved difficult due to the diversity of health landscapes across Europe. For instance, the exact definition of a paediatric centre may have varied by country, introducing a certain degree of measurement error to our survey results. On the other hand, other country level variables used in these analyses were collected in a highly standardized manner by umbrella organizations such as the World Bank for the purpose of country comparisons.
Missing data exist in various forms; missing completely at random, missing at random, and missing not at random. If patients with missing data differ from those with complete data (i.e. missing not at random), particularly regarding exposure and outcome variables, estimates will be biased, especially given that we limited our analysis to complete cases only [266]. Furthermore, as not all potentially confounding variables were collected by the registry, and as data collection for some variables was incomplete, missing data may have led to some degree of residual confounding, and prevents us from inferring causality.

Differences in country registry practice may have introduced missing data bias to our country comparison studies. This may have influenced our results regarding country mortality risk and incidence rates. Moreover, in some countries, children may be sent abroad for treatment. For instance, paediatric patients in Iceland are sent to Scandinavian countries for transplantation. Especially in some smaller Eastern European countries with limited facilities, the more complex children may be sent abroad for RRT. Therefore, dependent on how national registries approach the registration of cross-border care, this may also have affected the reliability of our incidence and mortality risk estimates.

Dialysis modality choice in children depends on many factors, such as physician and family preference, the type and severity of comorbidities present, the presence of various contraindications, malnutrition, hypertension, and various metabolic factors. As these case-mix variables are not all collected by the registry in all countries, and as sicker and more complex patients may be selected to start on HD as initial modality choice, this may have introduced selection bias to our results, and prevents us from inferring causality between initial dialysis modality and mortality risk.

Germany and Italy collect data on either transplant or dialysis patients. Therefore, including these countries would have introduced bias to our results; overall RRT incidence in these countries would have been underestimated, and as transplant patients have better survival rates compared to dialysis patients, our survival rates will have been skewed. It was therefore necessary to exclude Germany and Italy, which reduced the statistical power of our analyses and limited our ability to extrapolate our results across the whole European continent.
In some countries adolescents are lost to follow-up when transferred to adult care, whereas in other countries they are followed-up. This limits our ability to produce long-term outcome data for this age group. Moreover, as some adolescents may have initiated RRT in adult centres, this may have led to underestimation of RRT incidence. To make matters even more complex, the age of transition varies between countries and patients and often more complex high-risk patients, for example, those with severe comorbidities or cognitive disorders may be kept longer in paediatric care.

Lastly, in our survey, the explanatory factors collected reflect the situation in each country as of 2013, whilst the incidence rate was calculated over the period of 2007–2011. As some of the collected indicators may vary over time, this may therefore have influenced the accuracy of our results regarding associations between incidence rates and collected indicators.

**RECOMMENDATIONS FOR FURTHER RESEARCH**

We demonstrate that public health expenditure forms the main determinant of quality and access to RRT. Nonetheless, more research is needed to understand the exact mechanisms through which macroeconomics affect access and quality of care in countries with limited public health funding. This is problematic to approach through ecological study designs, and calls for a more country-specific, perhaps qualitative or mixed-methods, approach. Only after understanding the causal pathway on the country-level, can we explore potential strategies to help reduce these disparities.

Similarly, we still do not understand which mechanisms explain the associations between country neonatal mortality and RRT mortality and incidence rates. Neonatal mortality is used as a proxy for the quality of country paediatric, obstetric, and perinatal care, and therefore comprises various elements of health care. The neonatal mortality rate may be dependent on the organization of specialized paediatric care, the level of education for paediatricians and neonatologists, and population-related factors such as maternal health behaviours and the intrinsic health status of children. Moreover, the ethical decision to treat neonates at the limit of viability may also differ between countries, which will likely also affect the neonatal mortality rate. Consequently, it is challenging to pinpoint which components of neonatal
mortality are responsible for the associations with access to RRT and quality of care in our population, and certainly warrants further investigation.

We demonstrate that patients selected to start dialysis on PD have better survival probabilities compared to those selected to start on HD. Nonetheless, the proportion of children starting dialysis on PD varies widely across Europe (IQR 32%-67%). Although differences in age distribution (the youngest are preferentially started on PD) and the competing risk of transplantation may in part explain this variation, further study is necessary to explore the potential reasons underlying these differences, especially given the benefits of the PD first strategy.

We demonstrate a dialysis modality treatment effect predominantly in poorer European countries, and less so in affluent European countries. It remains unknown whether this is due to either a poorer performance on HD in poorer countries, or that these patients are sicker at treatment initiation and are therefore started on HD. Further research is required to determine explanatory factors and identify opportunities to intervene. As the majority of excess mortality occurs in these poorer countries on HD, strategies to improve survival in this population would contribute substantially to eliminating disparities in mortality risk across Europe.

More research is required to determine how specialized paediatric centres (for the treatment of rare diseases) should be organized within each country and across Europe, and how this would impact access to RRT and quality of RRT. Theoretically, the centralization of centres would force a larger volume of patients per centre and enable paediatric nephrologists to gain more experience, which may subsequently improve the quality of care. This may be especially effective regarding the transplantation of the youngest patients, which requires a highly specialized team and facilities. On the other hand, centralization of health services for rare disease may limit access to care, and is currently topic of debate [267].

We demonstrate the contemporary effect of macroeconomics on RRT incidence and mortality rates. However, it remains unknown how changes in country economics over time, such as
caused by the economic crisis, impact the quality of and access to paediatric renal care across Europe.

We used the time under treatment of a nephrologist as a proxy for timely referral and the speed of disease progression. Further research is required to disentangle these two aspects and their modifying effects on the relationship between dialysis modality choice and mortality. As access type modifies the relationship between dialysis modality choice and mortality, is related to the timeliness of referral, and differs between countries, this factor should also be taken into account when studying these effects [190, 268].

The primary outcome in our longitudinal studies included in this thesis is 5 year survival. Although the majority of deaths occur during the initial period of RRT, long-term survival data is still required as ESRD is a life-long condition. In contrast to adult patients, virtually all children with ESRD are considered transplantable. Consequently, long-term dialysis data are generally scarce and subject to negative selection of non-transplantable patients. Taking the latter into account, further data collection and research are required to provide nephrologists with the evidence necessary to answer patient and family questions regarding long-term outcomes.