# European disparities in the incidence and outcomes of children with end-stage renal disease

Chesnaye, N.C.

**Publication date**
2017

**Document Version**
Other version

**License**
Other

# 4

# Mortality risk disparities in children receiving chronic renal replacement therapy for the treatment of end-stage renal disease across Europe: An ESPN-ERA/EDTA Registry analysis

**Nicholas C Chesnaye**, Franz Schaefer, Marjolein Bonthuis, Rebecca Holman, Sergey Baiko, Esra Baskın, Anna Bjerre, Sylvie Cloarec, Elisabeth AM Cornelissen, Laura Espinosa, James Heaf, Rosário Stone, Diamant Shtiza, Ilona Zagozdzon, Jérôme Harambat, Kitty J Jager, Jaap W Groothoff, Karlijn J van Stralen

*The Lancet 2017 May; 389(10084): 2128-2137*

## ABSTRACT

**Background:** We explored the variation in country mortality rates in the paediatric population receiving renal replacement therapy (RRT) across Europe, and estimated how much of this variation could be explained by patient-level and country-level factors.

**Methods:** In this registry analysis, we extracted patient data from the ESPN/ERA-EDTA Registry for 32 European countries. We included incident patients younger than 19 years receiving RRT. Adjusted hazard ratios (aHR) and the explained variation were modelled for patient-level and country-level factors with multilevel Cox regression. The primary outcome studied was all-cause mortality while on renal replacement therapy.

**Results:** Between Jan 1, 2000, and Dec 31, 2013, the overall 5 year RRT mortality rate was 15.8 deaths per 1000 patient-years (IQR 6.4–16.4). France had a mortality rate (9.2) of more than 3 SDs better, and Russia (35.2), Poland (39.9), Romania (47.4), and Bulgaria (68.6) had mortality rates more than 3 SDs worse than the European average. Public health expenditure was inversely associated with mortality risk (per SD increase, aHR 0.69, 95% CI 0.52–0.91) and explained 67% of the variation in RRT mortality rates between countries. Child mortality rates showed a significant association with RRT mortality, albeit mediated by macroeconomics (eg, neonatal mortality reduced from 1.31 [95% CI 1.13–1.53], p=0.0005, to 1.21 [0.97–1.51], p=0.10). After accounting for country distributions of patient age, the variation in RRT mortality rates between countries increased by 21%.

**Interpretation:** Substantial international variation exists in paediatric RRT mortality rates across Europe, most of which was explained by disparities in public health expenditure, which seems to limit the availability and quality of paediatric renal care. Differences between countries in their ability to accept and treat the youngest patients, who are the most complex and costly to treat, form an important source of disparity within this population. Our findings can be used by policy makers and health-care providers to explore potential strategies to help reduce these health disparities.

## RESEARCH IN CONTEXT

### Evidence before this study

We searched Pubmed with the terms "paediatric", "renal replacement therapy", "end-stage renal disease", "variation", "mortality", "economic", "disparities". We set no limit for language of publication and searched for articles published up to 22 March 2016. All relevant publications were reviewed. International variation in mortality rates in the adult renal replacement therapy population has previously been attributed to both country and patient level determinants. In the paediatric population, a single study demonstrated that country mortality rates in patients treated with peritoneal dialysis were strongly affected by country gross national income.

### Added value of this study

We describe considerable international disparities in mortality risk in the paediatric renal replacement therapy population across 32 European countries. These disparities were largely explained by differences in public health expenditure, which seems to limit the availability and quality of paediatric renal care. We also demonstrate that country differences in their ability to accept and successfully treat the youngest patients, who are the most complex and costly to treat, formed an important source of disparity within our population.

### Implications of all the available evidence

By exploring the magnitude of health-care inequalities, and by identifying both patient- and country-level determinants, we hope to increase the awareness amongst policy makers and in the paediatric nephrology community, and explore potential strategies to help reduce these disparities. Considering the austerity-driven cuts in healthcare budgets experienced by most European countries over the past few years, our results pose a challenge for health care policy makers in their aim to ensure universal access to high-quality healthcare across Europe.

## INTRODUCTION

Considerable international and regional variation in mortality rates has been observed in the adult renal replacement therapy (RRT) population. Both patient and country-level factors may explain this variation. Differences in country macroeconomics, general population mortality, patient demographics, the distribution of cause of renal disease, the quality of renal care, access to treatment, and attitudes regarding acceptance to and withdrawal from treatment have been described as country-level factors explaining differences in mortality in the adult RRT populations [20–22].

In contrast to the adult patient population, European variation in paediatric RRT mortality rates has not previously been described due to the rarity of end-stage renal disease (ESRD) in children and the high survival rates, which makes it difficult to provide statistically robust estimates. Extrapolation from the adult to the paediatric RRT population is hampered by the facts that children suffer from different underlying causes of renal disease with a preponderance of genetic and other congenital causes, and that RRT provision to children is resource-intensive as they are generally treated in specialized (academic) paediatric facilities by extensive multidisciplinary teams [12].

To our knowledge, comparing mortality rates in children treated for a chronic disease has not previously been studied on a European scale. By exploring the magnitude of health-care inequality, and by identifying explanatory factors, we hope to increase the awareness amongst policy makers and in the paediatric nephrology community, and explore potential strategies to help reduce these disparities. The current paper therefore aims to 1) describe mortality rates in the paediatric RRT population across European countries, 2) study the relationships of, and potential interactions between, patient- and country-level factors with mortality rates, and 3) quantify how much of the variation in mortality rates is explained by these factors.

## METHODS

### Study population

The European Society for Paediatric Nephrology / European Renal Association – European Dialysis and Transplant Association Registry (ESPN/ERA-EDTA) was established to consolidate data collected by European population-based national renal registries on children with end-stage renal disease treated with renal replacement therapy. Data is collected annually in a standardized manner on various patient- and treatment characteristics and is subject to regular data quality checks both on the national as well as the Registry level [51]. We included incident patients under the age of 19, starting RRT between January 1, 2000, and December 31, 2013 for 32 European countries. . Austria (AT), Belgium (BE), Croatia (HR), Denmark (DK), Finland (FI), Greece (GR), Iceland (IS), the Netherlands (NL), Norway (NO), Spain (ES), Sweden (SE), Switzerland (CH), and The United Kingdom (UK) provided data from January 1, 2000, to December 31, 2013. France (FR) from 2004, Czech Republic (CZ), Hungary (HU), Lithuania (LT), Macedonia (MK), Portugal (PT), Romania (RO), Russia (RU), Serbia (RS), Slovakia (SK), and Slovenia (SI) from 2007, Belarus (BY), Bulgaria (BG), Estonia (EE), Montenegro (ME), and Poland (PL) from 2008, Albania (AL) and Ukraine (UA) from 2010, and Bosnia & Herzegovina (BA) from 2011. As Germany reported only on transplant patients and Italy reported only on patients starting on dialysis, these countries were excluded from the analyses.

### Patient and country-level determinants

The primary outcome studied was all-cause mortality on RRT. Follow-up time was censored when renal function recovered, patients were lost to follow-up, reached the end of study, or after 5 years of follow-up. We developed a conceptual framework (Appendix 1) describing the hypothesized causal pathways between various country- and patient-level factors and country RRT mortality rates (adapted with permission from Kramer et. al.[20]). Potential variables explaining the variation in mortality between countries were defined *a priori* and collected on the individual patient level as well as on the country level. On the patient level, data were extracted from the ESPN/ERA-EDTA Registry database on patient age at RRT initiation, gender, primary renal disease (PRD), time under treatment of a nephrologist prior to RRT, and initial treatment modality. We assumed a non-linear association between age and mortality based on previous reports [8, 79], an assumption which was confirmed by the analysis of our

own data. We therefore chose to use clinically relevant age groups, defined as starting RRT between the ages 0-1, 2-5, 6-12, and 13-18, instead of continuous age. PRDs were classified following the ERA-EDTA grouping of PRD codes for children[54]. Country-level data were extracted from the World Bank Database for each country and averaged for the corresponding years that patient data were collected (Appendix 2). Country-level data on RRT incidence, transplantation rate, and the proportion of pre-emptive transplants was extracted from the ESPN/ERA-EDTA Registry, whereas the number of centres providing paediatric RRT (available for 29 countries) and reimbursement rates (available for 20 countries) were collected through a previously conducted online survey, which is described in detail elsewhere [93]. The number of paediatric nephrologists per million children was extracted for 29 countries from a paper by Ehrich et al [81], where a paediatric nephrologist was defined as a paediatrician working full time in general paediatric nephrology, dialysis and paediatric renal transplantation. There were no missing values for patient-related variables, except for the variable "time under treatment of a nephrologist prior to RRT start" (available for 20 countries, N=2928). Analyses were restricted to complete cases only.

**Statistical analysis**

Crude country RRT mortality rates were calculated by dividing the number of deaths by the number of patient follow-up years and are displayed using a funnel plot. Funnel plots allow an objective comparison of institutional performance [94]. We compared individual countries' mortality rates using control limits to indicate the expected limits of random deviation from the overall European mortality rate[94]. The control limits were calculated by assuming that the number of deaths in a country followed a Poisson distribution with parameter equal to the overall European mortality rate multiplied by the observed number of years of follow-up in that country. Country names are abbreviated using 2 digit ISO codes.

As country variation in mortality rates may be attributed to both country-level factors and to country differences in the effect of patient characteristics, we adopted a multi-level approach using a Cox regression random effects model (shared frailty model). In this model, the baseline hazard of a country is modelled as the random effect (or frailty), and the effect of patient level covariates are allowed to vary by country. The random effect for each country represents the degree of deviation in mortality risk from the overall (European) mortality risk. The

heterogeneity in mortality risk between countries is reflected by the variance estimate of the random effect. The variance estimate in the empty model without covariates therefore represents the variation in country mortality risk. Adding an explanatory factor to the model, on either the country or the patient level, allows the variance estimate to be obtained adjusted for this factor. The proportional change in variance (PCV) after addition of an explanatory factor to the empty model therefore allows examination of its effect on the variation in mortality risk between countries. The PCV is calculated by simply subtracting the adjusted variance from the baseline variance and dividing by the baseline variance[95–98].

Using the same model, we were able to estimate both the crude and adjusted hazard ratio of each factor on country mortality. The proportional hazards assumption was graphically checked for all variables and accepted as not violated. The regression coefficients were standardized, removing the unit of measurement, thus improving the comparability of the hazard ratios over multiple measures. All variables were graphically checked for violation of the normal distribution and were not found to be severely skewed. Following an aetiological approach, we decided on which confounders to include in the multivariate models based on the conceptual framework (Appendix 1) and the criteria for confounding [99]. All analyses were performed with SAS version 9.3 .

Mortality rate estimates may be imprecise in smaller countries as increased variability is expected from smaller populations with limited follow-up time and events. As this may introduce noise into the results, we performed a sensitivity analysis excluding countries with less than 100 patient follow-up years; 22 out of 32 countries remained in the sensitivity analysis dataset (Austria, Belgium, Belarus, Croatia, Czech Republic, Denmark, Finland, France, Greece, Hungary, the Netherlands, Norway, Poland, Romania, Portugal, Russia, Serbia, Slovakia, Spain, Sweden, Switzerland, and The United Kingdom). In addition, as most countries report information collected from paediatric centres, older children treated in adult centres may be missed by the registry. To avoid potential selection bias caused by age differences between countries, we performed a second sensitivity analysis including only patients up to 14 years of age. Thirdly, as the youngest children intrinsically have the shortest time prior to RRT, we repeated this analysis excluding children under 2 years. Lastly, as some countries had incomplete coverage of the study period, we performed a sensitivity analysis including only

data from 2007 onwards and adjusted for calendar year. Results from all sensitivity analyses yielded similar variance estimates and hazard ratio profiles and were therefore not described in the results.

## RESULTS

### Country mortality

Between 2000 and 2013, 365 deaths were registered in 32 European countries during 23,078 years of patient follow-up in a total of 7108 patients, the equivalent of a crude 5-year mortality rate of 15·8 deaths per 1000 patient years. Country mortality rates (MR) ranged from 0·0 to 81·9 deaths per 1000 patient years (IQR 6·4 – 16·4 ) and are presented using a funnel plot (figure 1). Compared to the European average mortality rate, France (MR 9·2) performed more than 3 SDs better and The Netherlands (MR 9·4 ) performed more than 2 SDs better. Russia (MR 35·2), Poland (MR 39·9), Romania (MR 47·4), and Bulgaria (MR 68·6) performed more than 3 SDs worse compared to the European average, and Sweden (MR 26·0), Czech Republic (MR 38·6), and Bosnia and Herzegovina (MR 81·9) performed more than 2 SDs worse compared to the European average. The remaining countries did not differ from the European average any more than explained by random variation (figure 2). The number of deaths, follow-up years, and crude 5-year mortality rates are presented in Appendix 3.

As mortality is highest during the first year on RRT, and 5 years of follow-up was not available for all countries, we also studied 1-year mortality rates to avoid potential bias (whilst trading in statistical power). The crude 1-year European mortality rate was 32·6 deaths per 1000 patient years (215 deaths over 6600 years of patient follow-up). Compared to the European average mortality rate, France (MR 20·7) performed more than 2 SDs better, Russia (MR 72·8) and Romania (MR 84·1) performed more than 3 SDs worse, and Sweden (MR 60·8) performed more than 2 SDs worse compared to the European average (Appendix 4).

### Patient-level determinants

We explored how country differences in the effect and composition of patient level determinants would affect the variation in country mortality rates. The variation in country mortality rates increased after adjustment for patient age at RRT initiation (21%), the time

under treatment of a nephrologist prior to RRT start (available for 20 countries, N=2928, 29%), and PRD (8%). Conversely, country differences in the effect of initial RRT treatment modality reduced the variation in country mortality rates by 13%, whereas patient gender had no effect on the variation in country mortality rates (table 1). To illustrate using the example of patient age, Finland has a higher proportion of younger patients starting RRT (ages 0-2, 42·6%) compared to the European average (ages 0-2, 13·8%), and has a lower mortality risk in the youngest patients relative to the European average. As a consequence, the age-adjusted mortality risk will shift away from the European average, thus contributing to an increase in variation of RRT mortality risk between countries. The effect of patient age on the variation in country RRT mortality risk is visualized in figure 3.

**Figure 1.** Funnel plot displaying crude 5-year country mortality rates and aggregated regional mortality rates of paediatric patient on RRT. Each country mortality rate is plotted against the number of patient follow-up years. The latter is used to indicate the degree of reliability for the rate, as in countries with a small number of patients, estimates may be imprecise due to increased variability in smaller populations. The 95% and 99% control limits (which correspond to approximately 2 and 3 standard deviations, respectively) form a 'funnel' around the European average. Countries that fall outside these limits are doing either better or worse compared to the European average.

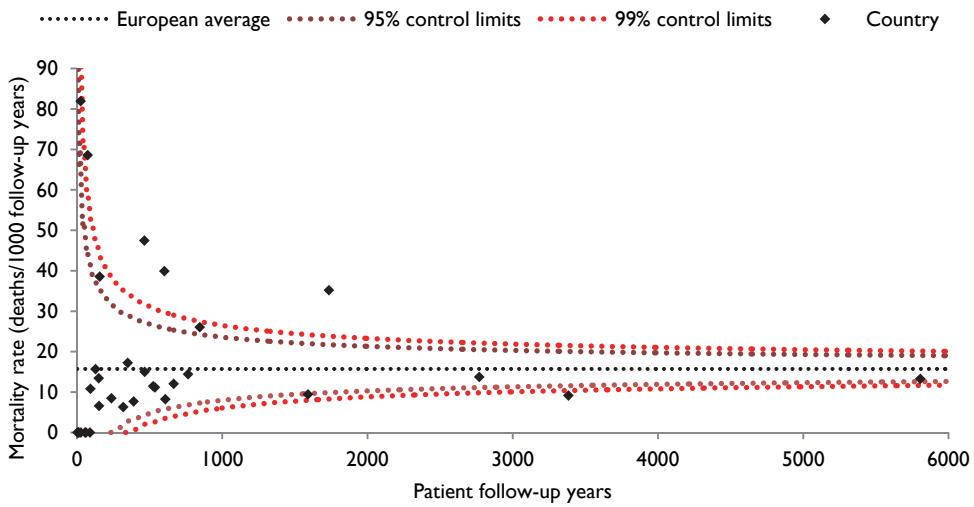


**Figure 2.** Spine plot displaying country crude 5-year country mortality rates, derived from the funnel plot. Mortality rates that lie within the central grey segment of the plot do not differ significantly from the European average. Countries that fall outside the 95% and 99% control limits (which correspond to approximately 2 and 3 standard deviations, respectively) are performing either better or worse compared to the European average.

**Table 1.** Univariate and multivariate hazard ratios for patient- and country-level determinants of mortality, and the effect of each determinant on the variation in country mortality rates. PCV = proportional change in variance. AH= antihypertensives. GH= growth hormone.

| | *Univariate* | | *Multivariate* | | | *Variation* | |
|---|---|---|---|---|---|---|---|
| | *HR (95% CI)* | *P-value* | *Confounders* | *aHR (95% CI)* | *P-value* | *Variance (SE)* | *PCV* |
| *Baseline model* | - | - | - | - | - | 0·24 (0·11) | Ref |
| *Macroeconomics* | | | | | | | |
| 1. GDP per capita (per1 SD increase) | 0·79 (0·62-1·02) | 0·07 | - | - | - | 0·18 (0·09) | -25% |
| 2. Public health expenditure (per1 SD increase) | 0·73 (0·61-0·86) | **<·0001** | 1 | 0·69 (0·52-0·91) | **0·008** | 0·08 (0·06) | -67% |
| 3. Private heath expenditure (per1 SD increase) | 0·88 (0·73-1·06) | 0·18 | 1 | 0·87 (0·74-1·03) | 0·11 | 0·22 (0·10) | -8% |
| *Child mortality* | | | | | | | |
| 4. Neonatal mortality rate (per1 SD increase) | 1·31 (1·13-1·53) | **0·0005** | 1,2 | 1·21 (0·97-1·51) | 0·10 | 0·12 (0·07) | -50% |
| 5. Under5 mortality rate (per 1 SD increase) | 1·32 (1·13-1·53) | **0·0004** | 1,2 | 1·21 (0·96-1·53) | 0·17 | 0·12 (0·07) | -50% |
| *Renal service indicators* | | | | | | | |
| 6. Paediatric RRT incidence (per1 SD increase) | 0·80 (0·63-1·02) | 0·07 | 1,2 | 1·02 (0·76-1·36) | 0·92 | 0·18 (0·09) | -25% |
| 7. Transplantation rate (per1 SD increase) | 0·85 (0·70-1·03) | 0·10 | 1,2 | 0·86 (0·70-1·06) | 0·16 | 0·19 (0·09) | -21% |
| 8. Proportion pre-emptive Tx (per1 SD increase) | 0·85 (0·71-1·02) | 0·07 | 1,2 | 1·00 (0·76-1·31) | 0·98 | 0·19 (0·09) | -21% |
| 9. No. centres pmc[x] (per1 SD increase) | 0·91 (0·75-1·10) | 0·31 | 1,2 | 0·92 (0·78-1·08) | 0·30 | 0·23 (0·11) | -4% |
| 10. No. paediatric nephrologists pmc (per1 SD increase)* | 0·93 (0·84-1·03) | 0·16 | 1,2 | 0·91 (0·85-0·98) | **0·02** | 0·25 (0·12) | 4% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11. Reimbursement AH** (for yes) | 0·98 (0·53-1·82) | 0·95 | 1,2 | 1·16 (0·72-1·87) | 0·53 | 0·30 (0·15) | 0% |
| 12. Reimbursement GH** (for yes) | 0·80 (0·33-1·96) | 0·62 | 1,2 | 1·49 (0·65-3·43) | 0·35 | 0·32 (0·15) | 7% |
| *Patient factors* | | | | | | | |
| 13. Age at RRT | | | 1,2,3,4,17 | | | 0·29 (0·12) | 21% |
| 0-1 years | 5·81 (4·34-7·78) | **<·0001** | | 6·49 (4·80-8·77) | **<·0001** | | |
| 2-5 years | 2·40 (1·69-3·41) | **<·0001** | | 2·60 (1·82-3·70) | **<·0001** | | |
| 6-13 years | 1·45 (1·06-1·98) | **0·02** | | 1·51 (1·10-2·07) | **0·01** | | |
| 13-18 years | Ref | Ref | | Ref | Ref | | |
| 14. Initial treatment modality | | | 1,2,3,4,12,17 | | | 0·21 (0·09) | -13% |
| HD | 2·91 (1·93-4·38) | **<·0001** | | 2·32 (1·53-3·52) | **0·001** | | |
| PD | 3·43 (2·29-5·12) | **<·0001** | | 1·76 (1·16-2·68) | **0·008** | | |
| Tx | Ref | Ref | | Ref | Ref | | |
| 15. Time under treatment prior to dialysis (per1 SD increase)*** | 0·54 (0·42-0·69) | **<·0001** | 1,2,3,4,13,17 | 0·88 (0·67-1·17) | 0·39 | 0·31 (0·23) | 29% |
| 16. Gender | | | - | | | 0·24 (0·11) | 0% |
| Female | 1·18 (0·96-1·44) | 0·13 | | - | - | | |
| Male | Ref | Ref | | Ref | Ref | | |
| 17. Primary renal disease | | | - | | | 0·26 (0·11) | 8% |
| Glomerulonephritis | 1·29 (0·93-1·80) | 0·12 | | - | - | | |
| Cystic | 1·13 (0·76-1·69) | 0·54 | | - | - | | |
| Hereditary | 1·60 (1·04-2·46) | **0·03** | | - | - | | |
| Ischemic | 1·91 (0·93-3·95) | 0·08 | | - | - | | |
| HUS | 1·19 (0·68-2·09) | 0·54 | | - | - | | |
| Metabolic | 1·65 (0·91-3·01) | 0·10 | | - | - | | |
| Vasculitis | 2·17 (1·13-4·16) | **0·02** | | - | - | | |
| Miscellaneous | 2·66 (1·91-3·70) | **<·0001** | | - | - | | |
| Unknown | 2·08 (1·46-2·97) | **<·0001** | | - | - | | |
| CAKUT | Ref | Ref | | Ref | Ref | | |

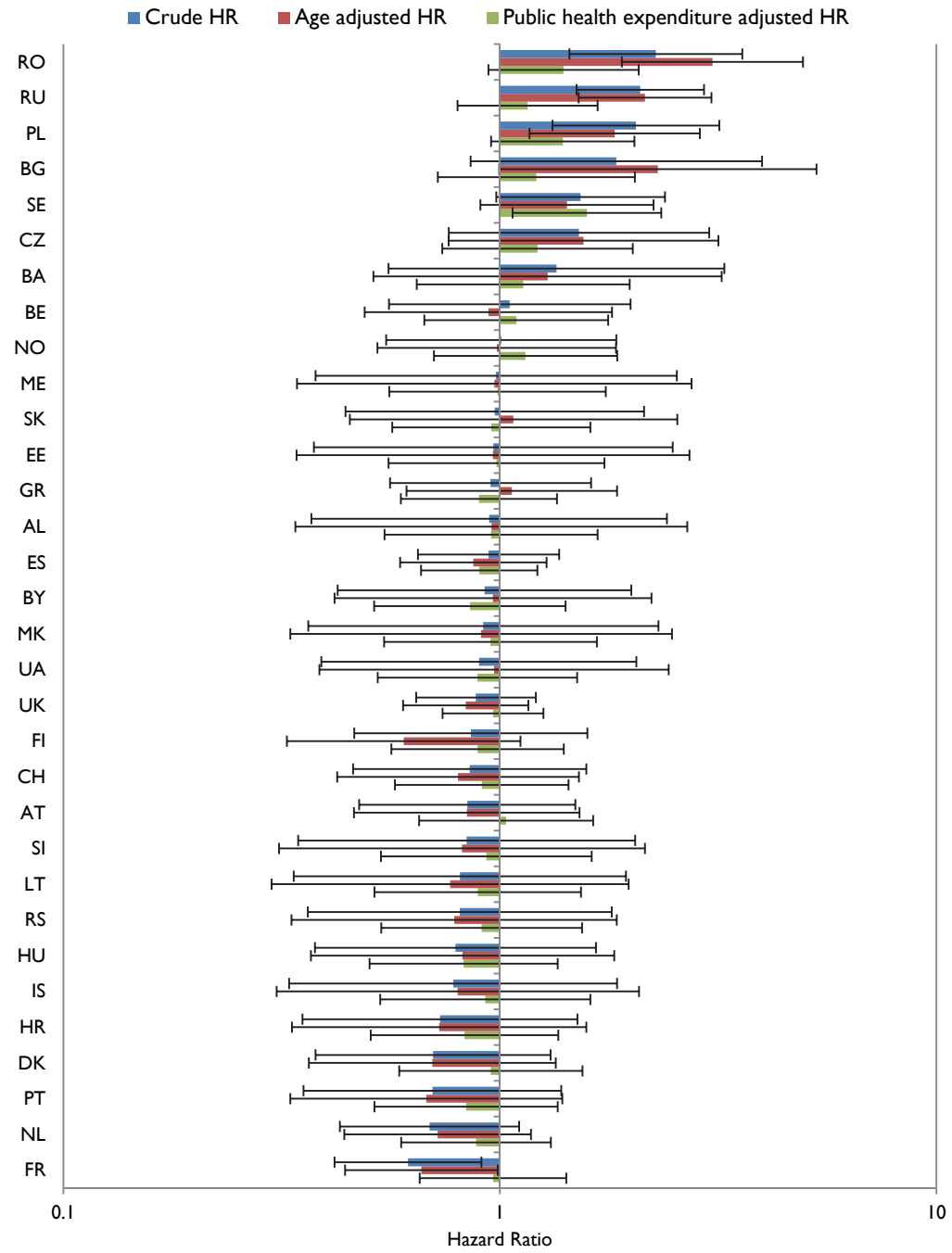
**Country-level determinants**

We studied the effect of country macroeconomics, country child mortality rates, and renal health service indicators on mortality risk and their influence on the variation in country mortality rates (table 1). An increase in country public health expenditure was strongly associated with a decreased mortality risk (aHR per SD increase: 0·69, 95% CI 0·52-0·91), and explained 67% of the variation in country mortality (visualized in figure 3), whereas private health expenditure (HR per SD increase: 0·88, 95% CI 0·73-1·06) had no significant effect. An increase in GDP per capita (HR per SD increase: 0·79, 95% CI 0·62-1·02, p=0·07, explained 25%) showed a protective trend with mortality risk. After adjustment for patient age distribution (not as a confounder, but as a mediator), this association reached statistical significance (aHR per SD increase: 0·74, 95% CI 0·58-0.96, p=.02), suggesting that a lower acceptance of high risk young patients in countries with limited resources may be somewhat masking the relationship between GDP and mortality. Increases in both neonatal (HR per SD increase: 1·31, 95% CI 1·13-1·53) and under 5 (HR per SD increase: 1·32, 95% CI 1·13-1·53) mortality rates were associated with an increased mortality risk, and explained 50% of the variation in country mortality rates. However, these latter effects were reduced after adjustment for macroeconomic factors (aHR per SD increase neonatal mortality: 1·21, 95% CI 0·97-1·51, under 5 mortality: 1·21, 95% CI 0·96-1·53). Similarly, the protective trends found between mortality risk and RRT incidence and the proportion of pre-emptive transplantations were also reduced after adjustment for country macroeconomics.

**Interactions between country-level and patient-level determinants**

We identified an interaction between country GDP per capita and initial dialysis modality. In the wealthiest countries, with a GDP per capita of more than $35 000 (AT, BE, CH, DK, FI, FR, IS, NL, NO, SE, UK), there was no significant mortality risk difference between initial dialysis modalities (HD vs. PD, aHR: 1·24, 95% CI 0·89-1·73, adjusted for age at RRT, PRD, gender), whereas in countries with a GDP per capita of less than $35 000, patients starting RRT on HD had an increased mortality risk compared to those starting on PD (HD vs. PD, aHR: 1·66, 95% CI 1·19-2·30), as illustrated by the Kaplan-Meier curves in figure 4. We found no other interactions between patient- and country level determinants.

**Figure 3.** Country unadjusted (blue), patient age adjusted (red), and public health expenditure adjusted (green) hazard ratios (exponentiated frailties) and 95% confidence intervals.



## DISCUSSION

Considerable variation exists in mortality rates of children treated with renal replacement therapy across Europe. Most of this variation was attributable to an increased mortality risk in several larger Eastern European countries compared to Northern, Southern, and Western European countries, where the mortality risk was mostly similar. The current study provides a novel disentanglement of the explanatory effect of both country and patient level factors on differences in country mortality risk. We demonstrate that country differences in the effect and distribution of patient characteristics, such as age at RRT onset, may conceal the true variation in country mortality risk, which we found to be primarily attributable to disparities in public health expenditure.

Economic welfare is a key determinant of health and access to health services. The effect of country macroeconomics on country RRT mortality risk in our population is understandable given the complexity and costs involved in the provision of renal care to children by a multi-professional paediatric team. Restricted public healthcare financing in particular is detrimental to the survival probabilities of children on RRT, whereas private, or out-of-pocket, health expenditure has little effect on mortality risk. This is not unexpected considering that the majority of paediatric patients are treated in (public) academic centers, and that most of the direct costs are fully reimbursed [93]. We also demonstrate an indirect effect of country macroeconomics on country mortality risk, as the effects of various renal service indicators and child mortality rates were attenuated after adjustment for macroeconomic indicators. Schaefer et al. previously demonstrated that country mortality rates in paediatric patients treated with PD were strongly affected by country gross national income (GNI), independent of patient age and the presence of comorbidities [23]. They included developing countries, and thus a wider range in both country GNI and mortality rates compared to our analyses of European middle- and high income countries. Nonetheless, despite the smaller range in country macroeconomics in our study, we demonstrate that health financing disparities across Europe are still adversely affecting mortality risk in the paediatric RRT population. Interestingly, the opposite effect of macroeconomics was previously demonstrated in the adult dialysis population, where a higher country GDP per capita and healthcare expenditure were associated with an increased country RRT mortality risk [20]. The authors attributed this association to a higher acceptance of patients with a poor health condition in wealthier

countries, and that increased health care spending does not necessarily result in more effective care. In children, where favourable macroeconomic conditions will also promote the inclusion of younger patients with severe comorbidities in RRT programs, resource spending appears to be more effective in terms of promoting patient survival.

The amplification of RRT mortality risk variation after adjusting for patient age demonstrates that countries differ in their ability to accept and successfully treat the youngest children, who are typically the most complex and costly to treat. We previously established a higher incidence of RRT in wealthier countries due to the acceptance of younger patients [93]. One may therefore expect a higher mortality rate in wealthier countries, as the youngest patients bear the highest mortality risk. Here we demonstrate the opposite, finding higher survival rates in wealthier countries despite the acceptance of younger and presumably more medically complex patients (i.e. Finland). Vice versa, lower survival rates were found in countries burdened with economic constraints, despite the lower acceptance of younger patients [79, 93]. This finding is a cause for concern, as non-acceptance to RRT implies an underestimation of ESRD mortality (as these patients go unregistered), thus further exacerbating the inequalities in care and mortality caused by economic disparities.

Interestingly, the high survival rate in pre-emptively transplant recipients was similar in both the wealthiest and less wealthy countries. Furthermore, 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 haemodialysis population. This may be due to either a poorer performance on HD in these countries, or that patients are sicker at treatment initiation and are therefore started on HD.

Child mortality rates reflect the health of the general paediatric population, as well as the level of economic development (for which we adjust in our multivariable analyses), and the accessibility and quality of paediatric (and obstetric) health services. Country-specific child mortality rates were associated with mortality on RRT and explained a large portion of the variation in country RRT mortality risk. This possibly reflects the impact of the quality of

paediatric health systems on the effectiveness of paediatric RRT care, as well as how the intrinsic mortality risk in the general paediatric population affects mortality on RRT [100]. However, the association was weakened after adjustment for macroeconomic factors, suggesting that the quality of country's paediatric health care system is - to some extent - reliant on country wealth and health expenditure.

The variation in paediatric RRT mortality rates was limited across Western, Northern, and Southern European countries. The majority of variation in mortality rates across Europe was attributable to several larger Eastern European countries, where patients had a significantly higher mortality risk compared to the European average. Since the fall of communism, many Eastern European countries have undergone dramatic changes in health care systems and financing, and have achieved substantial progress regarding the availability and effectiveness of renal services [81, 93, 101, 102]. Although the gap between Western and Eastern Europe has narrowed progressively over the past decades, many countries in Eastern Europe remain burdened under stringent austerity measures, limited health care budgets, and higher child mortality rates; factors which we demonstrate here to strongly affect the RRT mortality risk on a country level. Furthermore, after their accession to the EU, many Eastern and Central European countries experienced an outflow of health professionals to higher-income countries, and a consequent loss in educational health care investment [103–105]. This may cause larger problems in the future, given the inverse association found between RRT mortality and the number of paediatric nephrologists. In support of this premise, we found a positive trend ($p=0{\cdot}06$, independent of patient age) between the number of paediatric nephrologists in a country and the time under treatment of a nephrologist prior to RRT (as a marker for timely referral and speed of disease progression).

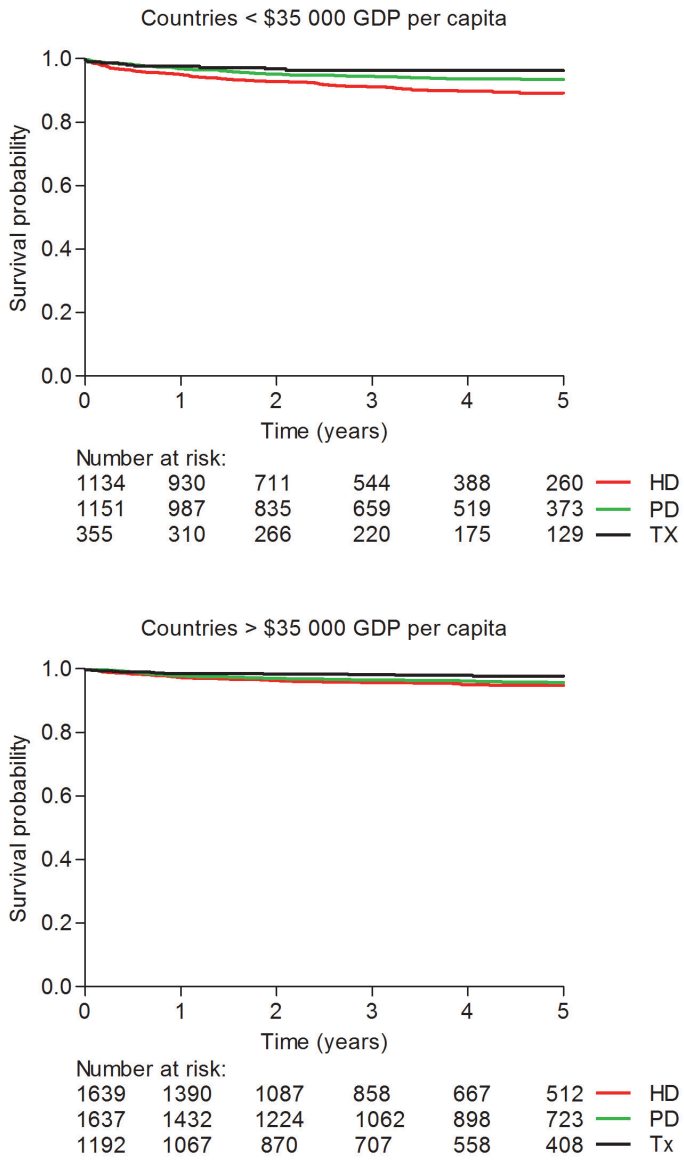
The study strengths include its large sample size, low loss to follow-up, and the European-wide inclusion of patients. Additionally, patient variables such as gender, primary renal disease, and treatment modality are collected by the registry in a standardized manner using an uniform coding system. Likewise, country level indicators are collected through umbrella organizations such as the World Bank for the purpose of country comparisons. Furthermore, the funnel-plot and frailty model techniques both provide a novel approach to describe and explain variation in paediatric RRT survival between countries. An important limitation is the lack of data

regarding children with ESRD who were not registered due to various reasons; 1) patients who were not accepted on RRT (i.e. in children with severe comorbid conditions and a perceived unacceptable quality of life), 2) patients who died prior to treatment initiation, or 3) patients who did not fulfill the national registry inclusion criteria. Other limitations include the incomplete coverage of the study period for several countries (although including data from 2007 onwards had no meaningful effect on the estimates), and a low number of events and follow-up time in smaller countries, which may impact the reliability of our country mortality rates due to random variation. Unfortunately, Germany and Italy were excluded from the study due to the fact that either transplant or dialysis patients are exclusively registered, and not the full RRT population. As transplant patients have higher survival rates compared to dialysis patients, including these countries would have introduced bias to the results. Lastly, multiple testing may form an issue in table 1, where the association between mortality risk and multiple indicators is tested, however, even if we were to use a more conservative p-value (for instance 0.01 instead of 0.05), this would not alter the interpretation of the results.

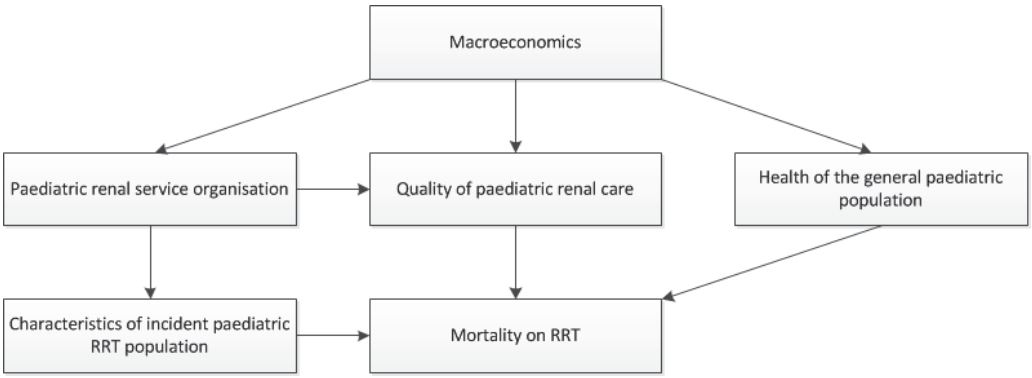
Although all European Union Member States have made commitments towards reducing inequalities in access to health care and in health outcomes, considerable international variation persists in mortality rates in the paediatric RRT population across Europe, most of which was attributable to an excess mortality risk for patients treated in several Eastern European countries. The majority of this variation was explained by disparities in public health expenditure, which seems to limit the availability and quality of paediatric renal care. Moreover, country differences in their ability to successfully treat the youngest patients, who are typically the most complex and costly to treat, seemed to be an important source of disparity within Europe. These results call for improvements to be made on both clinical- and policy-levels to reduce inequities in RRT mortality rates. To achieve this, we advocate further standardization of treatment guidelines and medical training for paediatric nephrologists across Europe, for example through the European Society for Paediatric Nephrology (ESPN) recommendations for the training of Paediatric Nephrologists, information exchange through international fellowships, and the provision of Continuing Medical Education courses [106]. Furthermore, in line with previous EU commitments, we recommend that national and European policy-makers involved in health care financing should pursue a uniform and high

quality of paediatric renal care across Europe, although this may prove challenging with varying national health priorities, especially in times of austerity.

**Figure 4.** Adjusted Kaplan-Meier plot for survival by initial treatment modality, stratified by GDP per capita, using covariate values, PRD group = CAKUT, gender = male, age group at RRT initiation = 6-12 years. HD = haemodialysis, PD= peritoneal dialysis, Tx = pre-emptive transplantation.



**Appendix 1.** Conceptual framework describing the hypothesized causal pathways between various country indicator groups and country RRT mortality rates, with macroeconomic indicators at the highest hierarchical level. We hypothesized that macroeconomics may affect RRT mortality rates through two main pathways. The first pathway assumes that macroeconomics dictate both organizational and quality aspects of paediatric renal care, for instance by influencing reimbursement rates (organizational) or the number of available treatment facilities (organizational), as well as the availability of a specialized multidisciplinary team (quality) or access to expensive medications such growth hormone therapy (quality). We hypothesized that organizational aspects of renal care may determine the characteristics of the paediatric RRT population in a country, such as the proportion of patients that receive a pre-emptive transplant or the average patient age at start RRT. The second pathway recognizes economic welfare as a key determinant of general population health, which consequently contributes directly to the intrinsic mortality risk in the paediatric RRT population.



**Appendix 2.** Description of country-level determinants.

| *Country Indicator* | *Description* |
|---|---|
| GDP per capita | Gross domestic product (GDP) per capita based on purchasing power parity (PPP), is a measure for country wealth. The PPP method allows for the international comparison of economies. |
| Public health expenditure | Public health expenditure consists is expressed as the percentage of national GDP that a government spends on health care. |
| Private health expenditure | Private health expenditure includes direct household (out-of-pocket) spending, and private insurance, expressed as a percentage of national GDP. |
| Neonatal mortality rate | Neonatal mortality rate is the number of neonates dying before reaching 28 days of age, per 1000 live births. |
| Under 5 mortality rate | Under 5 mortality rate is the number of children dying before reaching 5 years of age, per 1,000 live births. |
| Paediatric RRT incidence | Age-adjusted RRT incidence per million children under the age of 15. |
| Transplantation rate | The number of transplantations, pre-emptive or otherwise, expressed per million children. |
| Proportion of pre-emptive transplantations | The percentage of patients receiving a pre-emptive transplantation, as a proportion of all incident patients. |
| Centres providing paediatric RRT | The number of centres providing paediatric RRT, expressed per million children. |
| Number of paediatric nephrologists | The number of paediatric nephrologists per million children. |
| Reimbursement of anti-hypertensive medications | Reimbursement of anti-hypertensive treatment, defined as >90% reimbursement of costs. |
| Reimbursement of growth hormone treatment | Reimbursement of growth hormone treatment, defined as >90% reimbursement of costs. |

**Appendix 3.** Country 5-year mortality rates.

| *Country* | *N* | *Deaths* | *Follow-up years* | *Mortality rate* |
|---|---|---|---|---|
| AL | 6 | 0 | 13·2 | 0·0 |
| AT | 203 | 8 | 665·1 | 12·0 |
| BA | 18 | 2 | 24·4 | 81·9 |
| BE | 110 | 6 | 348·8 | 17·2 |
| BG | 34 | 5 | 72·9 | 68·6 |
| BY | 55 | 2 | 149·0 | 13·4 |
| CH | 141 | 6 | 536·7 | 11·2 |
| CZ | 70 | 6 | 155·6 | 38·6 |
| DK | 174 | 5 | 607·9 | 8·2 |
| EE | 3 | 0 | 8·9 | 0·0 |
| ES | 759 | 38 | 2768·6 | 13·7 |
| FI | 148 | 6 | 523·7 | 11·5 |
| FR | 1094 | 31 | 3383·3 | 9·2 |
| GR | 227 | 11 | 764·3 | 14·4 |
| HR | 82 | 2 | 318·3 | 6·3 |
| HU | 73 | 2 | 236·1 | 8·5 |
| IS | 23 | 0 | 89·0 | 0·0 |
| LT | 25 | 0 | 61·3 | 0·0 |
| ME | 3 | 0 | 2·6 | 0·0 |
| MK | 8 | 0 | 26·4 | 0·0 |
| NL | 460 | 15 | 1589·6 | 9·4 |
| NO | 129 | 7 | 466·2 | 15·0 |
| PL | 224 | 24 | 601·5 | 39·9 |
| PT | 129 | 3 | 390·0 | 7·7 |
| RO | 199 | 22 | 463·7 | 47·4 |
| RS | 47 | 1 | 152·0 | 6·6 |
| RU | 582 | 61 | 1733·9 | 35·2 |
| SE | 270 | 22 | 844·7 | 26·0 |
| SI | 17 | 0 | 55·3 | 0·0 |
| SK | 47 | 2 | 127·4 | 15·7 |
| UA | 32 | 1 | 92·5 | 10·8 |
| UK | 1716 | 77 | 5804·9 | 13·3 |

**Appendix 4.** Spine plot displaying country crude 1-year country mortality rates, derived from the funnel plot. Mortality rates that lie within the central grey segment of the plot do not differ significantly from the European average. Countries that fall outside the 95% and 99% control limits (which correspond to approximately 2 and 3 standard deviations, respectively) are performing either better or worse compared to the European average.