

# Factors associating with differences in the incidence of renal replacement therapy among elderly: data from the ERA-EDTA Registry

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## ABSTRACT

**Background.** The incidence of renal replacement therapy (RRT) in the general population aged 75 years or older varies considerably between countries and regions in Europe. Our aim was to study characteristics and survival of elderly RRT patients, and to find explanations for differences in RRT incidence.

**Methods.** Patients aged 75 years or older at the onset of RRT in 2010 to 2013, from 29 national or regional registries providing data to the European Renal Association- European Dialysis and Transplantation Association (ERA-EDTA) Registry, were included. Chi-square and Mann-Whitney-U tests were used to assess variation in patient characteristics, and linear regression was used to study the association between RRT incidence and various factors. Kaplan-Meier curves and Cox regression were employed for survival analyses.

**Results.** The mean annual incidence of RRT in the age group 75 years or older ranged from 157 to 924 per million age-related population. The median age at the start of RRT was higher and comorbidities were less common in areas with higher RRT incidence, but overall the association between patient characteristics and RRT incidence was weak. The unadjusted survival was lower in high-incidence areas due to higher age at onset of RRT, but the adjusted survival was similar (RR 1.00; 95% CI 0.97—1.03) in patients from low- and high-incidence areas.

**Conclusions.** Variation in the incidence of RRT among the elderly across European countries and regions is remarkable and could not be explained from the available data. However, the survival of patients in low- and high-incidence areas was remarkably similar.

**Keywords:** Elderly, ESRD, Europe, incidence, renal replacement therapy.

## INTRODUCTION

The European population is aging and the proportion of individuals aged 80 years or older has increased from 3.9% in 2004 to 5.1% in 2014 [1]. Simultaneously, the number of patients on renal replacement therapy (RRT) aged 75 years or older has nearly doubled, comprising 30% of all patients entering RRT in Europe. However, in 2014 the incidence of RRT per million age-related population (PMARP) among inhabitants aged 75 years or older varied considerably between European countries, ranging from 177 in Finland to 898 in Greece[2,3]. This has raised the question whether high incidence of RRT in the elderly population is related to widespread use of dialysis in frail patients with multiple comorbidities and poor survival.

Elderly RRT patients have inferior survival compared with younger patients [2,4] and cognitive decline as well as functional impairment and frailty are associated with adverse health outcomes [5]. The probability of receiving a kidney transplant is lower in the older age groups, whereas most elderly RRT patients are treated with in-center haemodialysis [2] which is the most expensive treatment modality [6]. As among elderly patients with comorbidities dialysis may not provide a survival advantage or improve health-related quality of life over conservative management of end-stage renal disease (ESRD) [7-9], careful selection of patients who are likely to benefit from RRT is essential.

The aim of this study was to search for explanations for the notable differences in RRT incidence in the elderly population by studying characteristics and survival of patients starting RRT in European countries.

## MATERIALS AND METHODS

Patients aged 75 years or older who started chronic RRT between 2010 and 2013 were identified from 13 national (Austria, Bosnia and Herzegovina, Denmark, Estonia, Finland, France, Greece, Iceland, Norway, Romania, Serbia, Sweden, and the Netherlands) and 16 regional (Dutch- and French-speaking Belgium, UK Scotland, and the Spanish regions of Andalusia, Aragon, Asturias, Basque Country, Cantabria, Castile and León, Castile-La Mancha, Community of Madrid, Catalonia, Extremadura, Galicia, Murcia, and Valencia) registries providing individual patient-level data to the ERA-EDTA Registry. Data were only available from Bosnia and Herzegovina and Serbia in 2011—2013, from Spain region of Murcia in 2012—2013, and from Estonia in 2013. Twelve registries (Austria, Dutch- and French-speaking Belgium, Denmark, Finland, Iceland, Norway, Sweden, and the Spanish regions of Aragon, Catalonia, Galicia, and Valencia) reported additional data on comorbidities at the start of RRT. Patients aged 20—74 were selected as a control group.

The incidence PMARP was defined as the number of patients starting RRT annually divided by the mid-year age-related general population. Patients were divided into two groups according to low

( $\leq 500$  PMARP) or high ( $> 500$  PMARP) registry-level incidence of RRT in the age group of 75 years or older. This division was selected to balance the number of patients and registries between low- and high-incidence groups.

Demographic and clinical variables such as age, sex, primary renal disease, initial RRT modality, survival, comorbidity (diabetes, ischemic heart disease, peripheral vascular disease, cerebrovascular disease, and malignancy), and body mass index (BMI) at the onset of RRT were correlated to the RRT incidence. Associations of life expectancy at birth [10] and gross domestic product (GDP) per capita [11] with RRT incidence were analysed. The reported causes of death were divided into eight groups, cardiovascular, cerebrovascular, infection, suicide / refusal or withdrawal from RRT, cachexia, malignancies, miscellaneous and unknown / unavailable.

When comparing distributions of variables between low- and high-incidence RRT registries, chi-square test was used for categorical variables and Mann-Whitney-U test for continuous variables. Linear regression was used to assess the association between continuous variables and RRT incidence by registry. Survival probability was assessed using the Kaplan-Meier method and differences in survival by the log-rank test, while the relative risk of death as a function of risk factors was estimated using Cox proportional hazards regression. Comorbidities were entered into the model as single items. Patients from Romania were excluded from the survival analysis because complete RRT history was not available for all patients. The survival time was calculated from the first day of RRT (dialysis or pre-emptive kidney transplantation) and the patients were followed until death ( $N = 19\,413$ ), censoring at loss to follow-up ( $N = 486$ ), recovery of renal function ( $N = 1\,079$ ), or end of the follow-up period on 31 December 2014 ( $N = 16\,632$ ). Two-sided P-values lower than 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 23.

## RESULTS

### Incidence

In the European countries and regions reporting individual patient data to the ERA-EDTA Registry, a total of 38 457 patients aged 75 years or older entered RRT between 2010 and 2013. The mean annual incidence of RRT in the age group 75 years or older, in 2010 to 2013, was 537 PMARP (Table 1). The incidence of RRT in the age group 20-74 years was 137 PMARP and varied considerably between countries and regions, ranging from 75 PMARP in Estonia to 175 PMARP in French-speaking Belgium. However, the difference between registries was much greater in the age group 75 years or older with the incidence of RRT ranging from 157 PMARP in Estonia to 924 PMARP in Dutch-speaking Belgium (Figure 1). The variation further increased in the age group 85 years or older, in which the incidence ranged from 27 PMARP in Spain (Cantabria) to 755 PMARP in Dutch-speaking Belgium. In the age group 75 years or older, the incidence rate ratio of RRT between men and women varied markedly, from 1.5 in Bosnia and Herzegovina to 4.4 in the

Basque Country. The incidence rate ratio of RRT between the age groups 75 years or older and 20-74 years was considerably larger in registries with higher incidence of RRT in the elderly (Table 1).

### Patient characteristics

Table 2 shows the characteristics of the patients in registries with low and high incidence of RRT. Twenty-two registries and 13 033 patients were included in the low-incidence group and seven registries and 25 424 patients in the high-incidence group. The median age of the entire cohort of patients 75 years or older was 80.5 (IQR 6.2) years at start of RRT. Patients from the low incidence areas were younger and more frequently had peritoneal dialysis as the initial treatment modality. Sex and BMI distributions were almost similar in both incidence groups. Hypertension was a more common cause of ESRD in the high-incidence compared with the low-incidence group. The rate of kidney transplantation within one year from the onset of RRT was small in this cohort of elderly patients, but was greater in the low- than the high-incidence group.

Registries with incidence of RRT in elderly patients in the upper range showed a significantly higher median age at the initiation of RRT, whereas the ratio between males and females, the life expectancy at birth, or GDP per capita of the area did not correlate with RRT incidence (Figure 2).

### Survival

Cardiovascular cause of death was most common in both incidence groups, 28.0% in the low-incidence group and 31.4% in the high-incidence group. The distribution of causes of death was different between the low- and high-incidence groups ( $P < 0.001$ ). The difference was mainly due to higher percentage of patients dying from cardiovascular and cerebrovascular causes in the high incidence registries and lower percentage of patients dying due to suicide or refusal or withdrawal of treatment.

Survival among the 36 807 patients aged 75 years or older was worse in the higher age groups. One-year survival from the onset of RRT was 74% (95% CI 73—74%) in the whole cohort and for the age groups 75-79 years, 80-84 years and 85 years or older the survival rate was 78% (95% CI 77—78%), 73% (95% CI 72—74%) and 66% (95% CI 65—68%) ( $P < 0.001$ ), respectively. Among patients older than 75 years, the 1-year survival was 76% (95% CI 75—76%) in the low-incidence group and 73% (95% CI 72—73%) in the high-incidence group ( $P = 0.04$ ) (Figure 3).

The relative risk of death was 1.03 (95% CI 1.002—1.065) in the high- compared with the low-incidence group. After adjustment for age and gender, there was no difference in survival between the low- and high-incidence groups (RR 0.97; 95% CI 0.94—1.00). Further adjustment for initial RRT modality and the cause of ESRD did not affect the relative risk of death (RR 1.00; 95% CI 0.97—1.03).

### Comorbidities

A total of 10 714 patients from 12 registries provided comorbidity data at the start of RRT. Basic characteristics of patients in registries with low and high incidence of RRT were similar compared to the whole cohort. Diabetes, ischaemic heart disease, cerebrovascular disease and malignancies were more common among patients in the low-incidence group, whereas peripheral vascular disease was more common in the high-incidence group (Table 2). In the low-incidence group, 76%

of the patients had at least one comorbidity at the onset of RRT compared with 63% in the high incidence group ( $P < 0.001$ ).

In survival analysis of patients who had data available on all five reported comorbidities ( $N = 9014$ ), the risk of death was lower in the high-incidence group (RR 0.76; 95% CI 0.71—0.80) than in the low-incidence group. All of the comorbidities and higher age at onset of RRT were associated with worse survival. When age at onset of RRT, sex and comorbidities were added into the multivariable model, the relative risk of death among patients in the high-incidence group did not change (RR 0.75; 95%CI 0.71—0.79).

## DISCUSSION

This study showed the incidence of RRT to vary significantly between European countries. Strikingly, in age group 75 years or older the difference between the countries with the highest and lowest incidence was almost sixfold, whereas among patients aged 20—74-years the difference was only twofold. We were not able to find any plausible explanations for this difference. Notably, there was no association between wealth, life expectancy, comorbidities or other patient characteristics and the incidence of RRT among the elderly. The only exception was age at the onset of RRT, which was greater in high-incidence areas. Our study also revealed that survival of the elderly patients was remarkably similar in the low- and high-incidence areas. In the subset of patients with available comorbidity data, the risk of death was higher in the low-incidence group, and this did not change after adjustments. This reflects the fact that the comorbidities, all of which were associated with worse survival, were surprisingly more common in the low-incidence group, despite the older age in the high-incidence group. This is in line with a study from France showing lower comorbidity among older age groups of dialysis patients [12]. Taken together, our findings suggest that differences in patient selection and timing of RRT may account for at least part of the observed variation in incidence.

The main strength of this study is the large and comprehensive cohort from the 29 registries that includes complete data on age, sex, primary renal diagnosis, initial RRT modality and survival. Hence, selection bias was minimal in the main analyses. By contrast, data on comorbidities were available from only 12 registries and were complete for only 84% of patients. Among these patients the risk of death was higher in the low-incidence registries in contrast to the results from the whole study population. This limitation may have introduced a bias into the analyses. The higher incidence of comorbidities in the low-incidence registries might reflect a higher prevalence of comorbid conditions in the general population in these countries. There could also be differences in the practice of collecting and reporting comorbidity data, or in evaluating predialytic patients for comorbidities between countries and regions. The proportion of patients who receive conservative treatment of kidney failure might also vary. The timing of the onset of RRT is likely to have an impact on the incidence of RRT among the elderly as their mortality rate is high and death is an important competing risk for starting dialysis [13-15]. Unfortunately we did not have

information on estimated glomerular filtration rate before the start of RRT or on the prevalence of predialytic renal disease to explore this issue. Notably, early start of RRT has not been shown to improve survival [16], and in fact an early start has been reported to associate with worse survival in elderly patients because of their high rate of comorbidity [17,18]. Variations in practice of acceptance of patients into RRT and conservative management, profit vs. non-profit haemodialysis facilities, pre-dialysis management, and competing mortality may all play an important role in explaining differences in RRT incidence, but these were not evaluated in this study.

Caskey and colleagues reported that GDP per capita and money spent on health care and dialysis facilities were positively associated with RRT incidence rates across 46 countries worldwide [19]. They also showed that higher incidence of RRT associates with private for-profit haemodialysis facilities in developed countries, which is in line with a study of conservative care for ESRD in 11 European countries [20]. We were unable to show an association between GDP per capita and RRT incidence in the aging population. This may potentially be due to smaller differences in GDP between the countries in our analysis. Furthermore, Visser and colleagues showed that the higher incidence of RRT in the elderly in Flanders compared with the Netherlands does not seem to be due to a more restrictive referral policy or lower access to RRT in the Netherlands. They suggested that the difference was more likely due to differences in comorbidity and life style [21,22].

The differences in RRT incidence among the elderly could be partly explained by diverse usage of conservative management in the care of patients with ESRD. A study from the UK revealed that there is much variation in the way conservative management of ESRD is provided in 67 UK renal units [23]. This variability may be even more notable between countries. Several studies have reported that dialysis improves the survival of elderly patients [24-26]. In addition, better management of patients during the progression of chronic kidney disease could reduce the number of comorbidities and increase the number of healthier elderly patients who benefit from dialysis [27]. However, when older age is combined with greater comorbidity, the prognosis is similar with dialysis and conservative management [9,28,29]. Despite this, the level of comorbidity had no effect on the decision to initiate dialysis in elderly patients in a recent study from United States [30]. Although dialysis improves the survival of elderly patients with ESRD, the treatment is associated with higher rates of hospitalization [31]. This together with the burden of dialysis therapy may explain why declining quality of life is frequently observed in these patients [25,32]. In fact, the quality of life is often better preserved in patients receiving conservative care for ESRD [24]. Consequently, dialysis should not be expected to improve the quality of life in elderly patients with comorbidity [8,25]. Information provided to patients by nephrologists and other renal unit staff plays an important role when older adults are choosing between dialysis and conservative management [33], but according to the study from the Netherlands the decision seems to be based on personal values, beliefs and feelings toward life, suffering, and expected difficulties on RRT, rather than on the effectiveness of the treatment [34]. Dialysis is expensive, especially among elderly, and is estimated to cost up to 90 000 euros annually for each patient [35]. Therefore, the decision to start dialysis in an elderly patient with substantial comorbidity should only be made after careful consideration and the patient should be involved in the decision-making [36,37].



## CONCLUSION

This European study shows that in areas with a high incidence of RRT among the elderly, the age at RRT start was slightly higher, while age-adjusted survival was similar compared with areas with low incidence. Data on comorbidities were available only for a subset of patients and comorbidities were more common in patients from the low-incidence areas. Factors explaining the differences in RRT incidence could not be elucidated and, therefore further studies are required. However, our findings may suggest that differences in patient selection and timing of RRT may explain some of the variation in incidence. An inappropriately high acceptance rate to dialysis is very costly for the society and may not improve survival or quality of life of patients. On the other hand, the criteria for initiating dialysis in elderly might be too strict in the low-incidence countries and regions. The fact that low or high incidence of RRT among the elderly is not associated with survival raises the question which policy is correct. More information is needed to guide treatment decisions for ESRD in the elderly.

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## CONFLICT OF INTEREST STATEMENT

None declared.

## AUTHORS' CONTRIBUTIONS

Jaakko Helve, Anneke Kramer, Kitty Jager, and Patrik Finne contributed to the literature search, study design, data collection, data analysis, data interpretation, and writing. All co-authors contributed to data collection, data interpretation, and writing. All authors have seen and approved the final version of the article.

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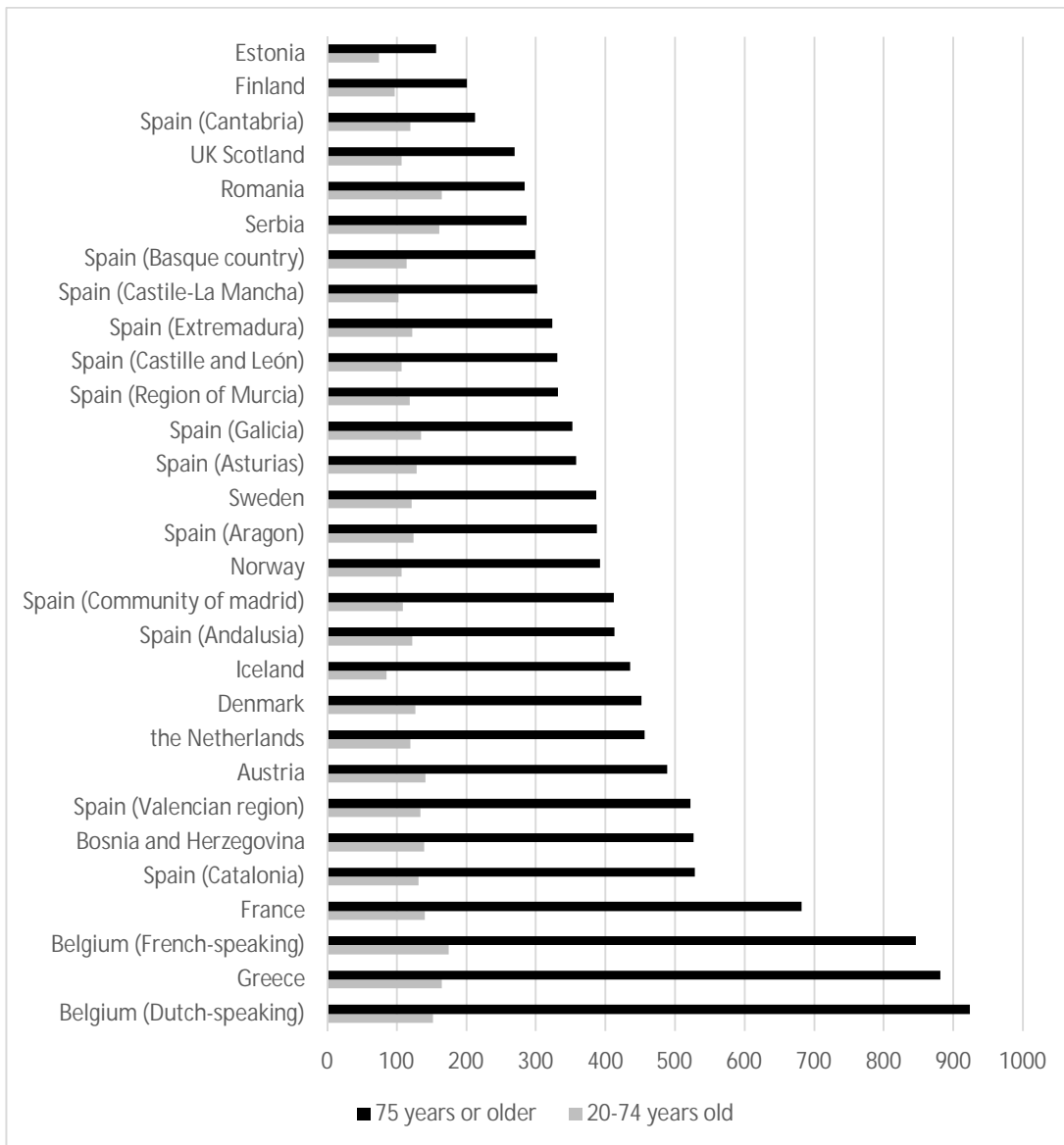
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Figure 1. Incidence of renal replacement therapy per million age-related population in 2010-2013, by age group



Data from Bosnia and Herzegovina and Serbia were available in 2011-2013, from Spain region of Murcia in 2012-2013, and from Estonia in 2013.

Table 1. Incidence of renal replacement therapy per year between 2010 and 2013 per million age-related population, by age group

	Number of patients $\geq 75$ years	RRT incidence of patients $\geq 75$ years PMARP		RRT incidence of patients $\geq 85$ years PMARP			$\geq 75 / 20-74$ years <sup>1</sup>	Male / Female <sup>2</sup>	
	All	Female	Male	All	Female	Male	All	All	
Belgium (Dutch-speaking)	2169	637	1361	924	478	632	755	6.1	2.1
Greece	3870	630	1223	882	559	711	751	5.3	1.9
Belgium (French-speaking)	1290	465	1532	846	348	511	620	4.8	3.3
France	15587	413	1128	678	338	482	574	4.8	2.7
Spain (Catalonia)	1404	325	858	529	138	250	268	4.0	2.6
Bosnia and Herzegovina	213	444	646	528	158	189	247	3.8	1.5
Spain (Valencian region)	891	338	800	523	149	195	231	3.9	2.4
Austria	1327	310	804	489	172	189	265	3.5	2.6
the Netherlands	2177	270	751	457	126	185	219	3.8	2.8
Denmark	721	257	742	451	161	242	276	3.6	2.9
Iceland	33	324	584	436	154	77	146	5.1	1.8
Spain (Andalusia)	1040	290	606	414	99	163	177	3.4	2.1
Spain (Community of Madrid)	823	239	710	413	59	168	160	3.8	3.0
Norway	553	208	679	392	113	178	199	3.6	3.3
Spain (Aragon)	236	209	656	389	42	85	84	3.1	3.1
Sweden	1247	219	635	387	112	180	194	3.2	2.9
Spain (Asturias)	196	204	619	358	84	159	170	2.8	3.0
Spain (Galicia)	485	191	613	353	64	94	109	2.6	3.2
Spain (Region of Murcia)	70	238	471	332	58	29	58	2.8	2.0
Spain (Castile and León)	446	193	537	331	95	147	159	3.1	2.8
Spain (Extremadura)	152	194	522	324	88	100	125	2.6	2.7
Spain (Castile-La Mancha)	253	227	407	302	13	94	68	2.9	1.8
Spain (Basque country)	272	131	577	299	46	64	78	2.6	4.4
Serbia	475	215	416	290	83	113	128	1.7	1.9
Romania	1650	174	447	282	45	96	91	1.8	2.6
United Kingdom, Scotland	448	181	409	270	64	44	73	2.5	2.3
Spain (Cantabria)	53	110	383	213	20	20	27	1.8	3.5
Finland	358	104	372	201	23	49	53	2.1	3.6
Estonia	18	109	280	157	0	48	38	2.1	2.6
All	38457	335	859	536	224	320	373	3.9	2.6

Data from Bosnia and Herzegovina and Serbia were available in 2011-2013, from Spain region of Murcia in 2012-2013, and from Estonia in 2013.

RRT, renal replacement therapy.

PMARP, per million age related population.

<sup>1</sup>Ratio of RRT incidence in  $\geq 75$  and 20-74 years old patients.

<sup>2</sup>Ratio of RRT incidence in male and female  $\geq 75$  years old.

Table 2. Characteristics of patients 75 years or older, divided into low- and high-incidence renal replacement therapy groups

	Low incidence (≤500 PMARP)	High incidence (>500 PMARP)	P-value
Number of patients	13 033	25 424	
Male (%)	62.2	61.2	0.045
Median age (years)	79.6 (IQR 5.4)	81.1 (IQR 6.5)	<0.001
85 years or older (%)	11.6	22.5	<0.001
Median Body mass index <sup>1</sup>	25.3 (IQR 5.7)	25.7 (IQR 6.1)	0.050
Initial RRT modality			
Haemodialysis (%)	87.3	90.4	<0.001
Peritoneal dialysis (%)	12.5	8.7	
Kidney transplantation (%)	0.2	0.1	
Missing (%)	0.0	0.7	
Kidney transplantation within one year (%)			
	0.7	0.3	<0.001
Primary renal disease			
Glomerulonephritis (%)	6.5	5.4	<0.001
Pyelonephritis (%)	5.4	4.2	
Polycystic renal disease (%)	2.2	1.9	
Diabetic nephropathy (%)	17.6	19.7	
Hypertension (%)	18.9	29.6	
Vascular disease (%)	8.4	3.3	
Other (%)	15.8	14.6	
Chronic kidney disease NAS (%)	24.1	21.2	
Missing (%)	1.1	0.0	
Comorbidity <sup>2</sup>			
Diabetes (%)	36.8	30.9	<0.001
Ischemic heart disease (%)	36.1	32.6	<0.001
Peripheral vascular disease (%)	21.5	25.3	<0.001
Cerebrovascular disease (%)	19.9	16.1	<0.001
Malignancy (%)	22.4	16.5	<0.001
Mean life expectancy at birth (years)	81.6 (IQR 2.0)	81.3 (IQR 1.8)	0.64
Mean gross domestic product per capita (US dollars)	26644 (IQR 17325)	23966 (IQR 15100)	0.82

PMARP, per million age related population; NAS, Aetiology uncertain / unknown; IQR, interquartile range

<sup>1</sup>Body mass index could be calculated for 2015 patients in the low-incidence group and 1837 patients in the high-incidence group.

<sup>2</sup>Available from Austria, Dutch- and French-speaking Belgium, Denmark, Finland, Iceland, Norway, Sweden, and the Spanish regions of Aragon, Catalonia, Galicia, and Valencia, 4960 patients in the low-incidence group and 5754 patients in the high-incidence group.

Figure 2. Association between explanatory factors and incidence of renal replacement therapy in patients 75 years or older

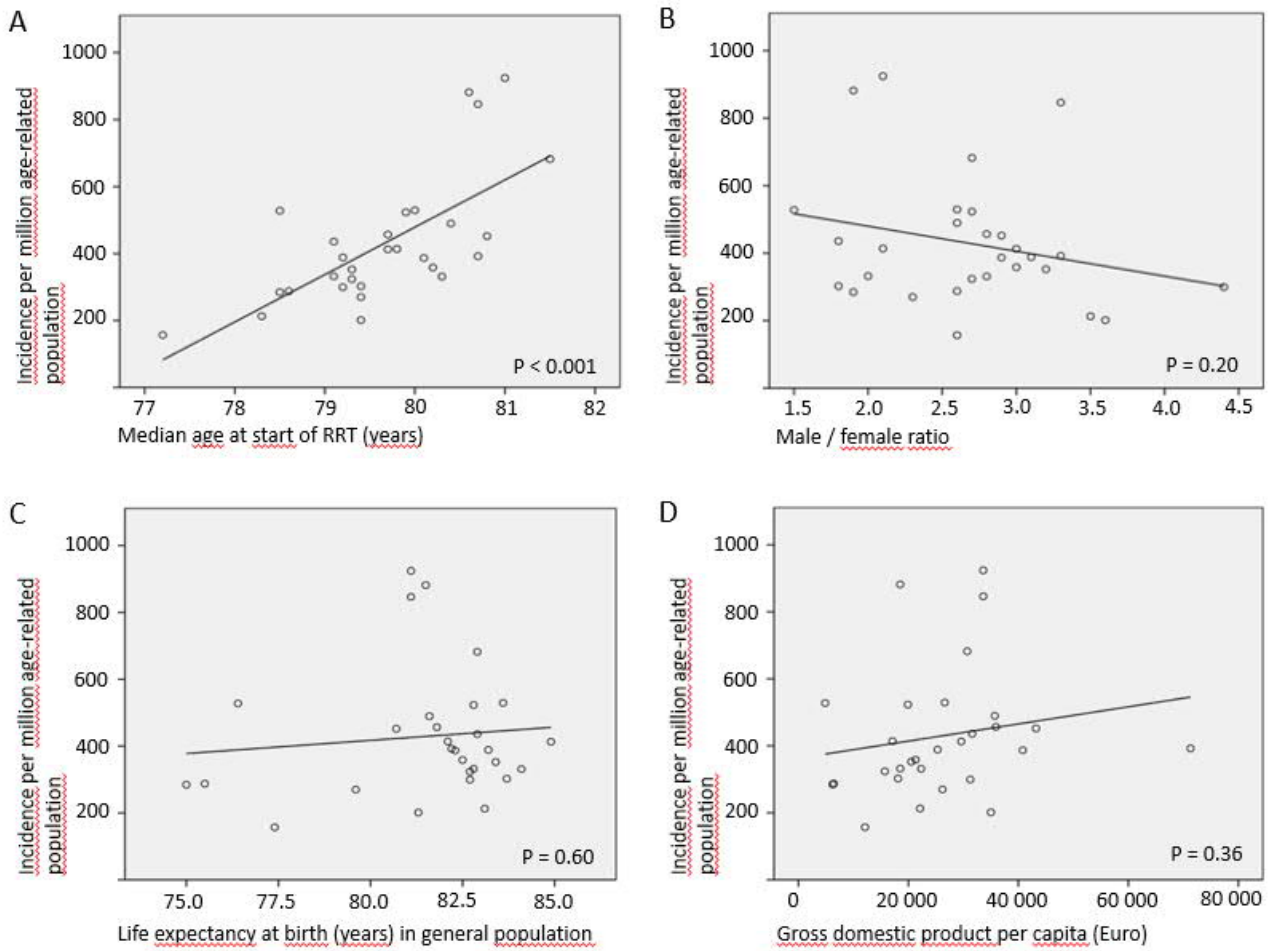




Figure 3. Survival from onset of renal replacement therapy, by low- and high-incidence renal replacement therapy groups

