Journal Pre-proof

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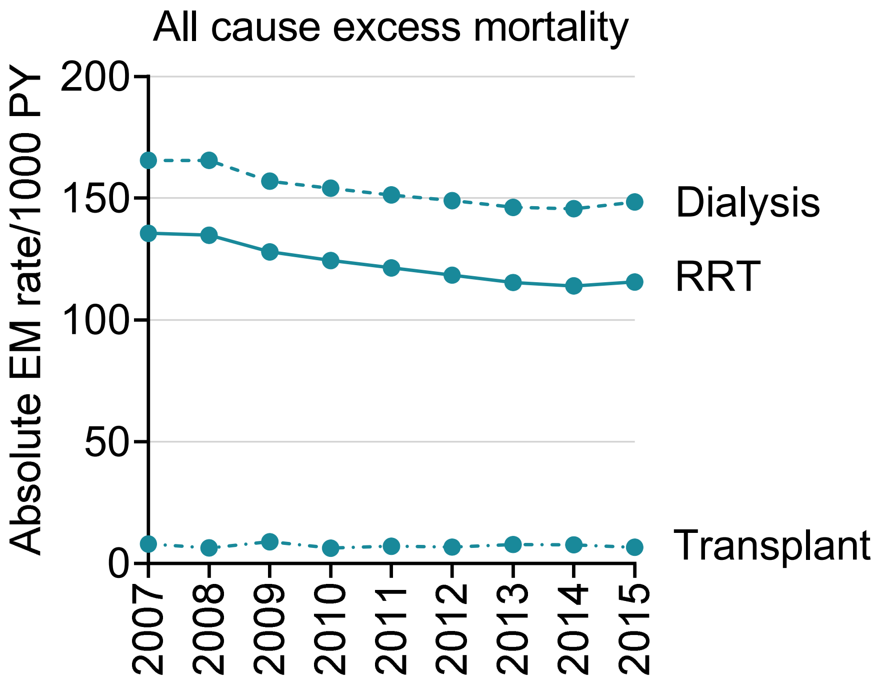
Does improvement in RRT survival only reflect better survival in the general population?

- ► Excess mortality (EM): mortality in RRT patients minus expected mortality in the matched general population
- ► Data from 280,075 incident adult RRT patients from 12 European countries



Cause of death	Relative EM risk per 5 year (95%CI)	
	Dialysis	Transplant
All-cause	0.86 (0.85 - 0.86)	1.16 (1.07 - 1.26)
Atheromatous CVD	0.72 (0.70 - 0.74)	1.29 (0.97 - 1.73)
Non-atheromatous CVD	0.90 (0.88 - 0.92)	1.00 (0.80 - 1.23)
Infections	0.90 (0.87 - 0.92)	0.99 (0.86 - 1.14)
Malignancies	0.95 (0.90 - 1.00)	2.51 (1.35 - 4.68)

CONCLUSION:
Survival on dialysis has improved more than in the general population, especially for atheromatous CVD. In transplant recipients, the EM risk increased, still the EM rate was low.

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Data from the ERA-EDTA Registry was examined for trends in excess mortality in European adults on kidney replacement therapy.

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Running headline

Excess mortality in European RRT patients.

Abstract

The objective of this study was to investigate whether the improvement in survival seen in patients on kidney replacement therapy reflects the enhanced survival of the general population. Patient and general population statistics were obtained from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry and the World Health Organization databases, respectively. Relative survival models were composed to examine trends over time in all-cause and cause-specific excess mortality, stratified by age and modality of kidney replacement therapy, and adjusted for sex, primary kidney disease and country. In total, 280,075 adult patients started kidney replacement therapy between 2002 and 2015. The excess mortality risk in these patients decreased by 16% per five years (relative excess mortality risk (RER)) 0.84; 95% confidence interval 0.83-0.84). This reflected a 14% risk reduction in dialysis patients (RER 0.86; 0.85-0.86), and a 16% increase in kidney transplant recipients (RER 1.16; 1.07-1.26). Patients on dialysis showed a decrease in excess mortality risk of 28% per five years for atheromatous cardiovascular disease as the cause of death (RER 0.72; 0.70-0.74), 10% for non-atheromatous cardiovascular disease (RER 0.90; 0.88-0.92) and 10% for infections (RER 0.90; 0.87-0.92). Kidney transplant recipients showed stable excess mortality risks for most causes of death, although it did worsen in some subgroups. Thus, the increase in survival in patients on kidney replacement therapy is not only due to enhanced survival in the general population, but also due to improved survival in the patient population, primarily in dialysis patients.

Keywords

Excess mortality, Renal Replacement Therapy (RRT), Kidney transplantation, Dialysis, Survival

Introduction

Patients with end-stage kidney disease (ESKD) are at a high risk of death. Even after starting renal replacement therapy (RRT), half of the patients will die within 5 years.[1] On the other hand, analyses of registry data have shown that patient survival on RRT has moderately improved over the last decades.[2-4] Part of this increase may reflect the overall increase in survival of the general population.

One way of comparing survival of the RRT population with that of the general population is by applying time-dependent relative survival models. For the United States RRT population, Foster et al. have recently applied these models to examine trends in excess mortality over time.[5] Excess mortality was defined as the mortality in the RRT population minus the expected mortality in the general population, matched for age, ethnicity, and sex. Their results showed that between 1995 and 2013 the excess risk of all-cause mortality among patients on RRT decreased for all age categories.[5] The results of this study, however, may not be generalizable to the European RRT population due to differences in case-mix, such as comorbidities, primary kidney disease distribution, and ethnicity, and differences in health insurance status, economic incentives and patient survival.[1,6-10]

Changes in excess mortality may differ by cause of death. In the general population, there was a decrease in death rates for malignancies and ischemic heart disease over the last decade, whereas a small increase was observed for infections.[11,12] Simultaneously, Pippias et al. showed that the risk of death in RRT patients decreased for cardiovascular diseases and infections, while among patients aged 65 years and older mortality due to malignancies increased.[4] However, Pippias et al. did not examine trends over time in cause-specific mortality in patients on RRT in relation to mortality trends in the general population.

Therefore, using the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry database, we aimed to examine trends over time in excess all-cause mortality and excess cause-specific mortality in patients on RRT, by subgroups of age and RRT modality. If we could show a larger improvement in the survival of RRT patients than in the general population, hence a decrease in excess mortality, this potentially indicates a better treatment of this patient group over time.

Results

In total, 280,075 adult patients initiated RRT between 1 January 2002 and 31 December 2015, contributing 1,031,390 person-years on RRT to the study, including 729,654 person-years on dialysis and 301,422 person-years with a functioning kidney transplant. Table 1 shows the patient characteristics by calendar period and age group. Most patients were male (63%) and diabetes mellitus was the most common cause of ESKD (21%). The case-mix of the study population when censored after 5 years of follow-up was similar to the total study population (data not shown). Even after censoring, the percentage of kidney transplant recipients slightly increased over time (Table 1). When compared to the uncensored results, the decrease in observed mortality rates were less pronounced in censored RRT patients. In the subgroup of transplant recipients, the increase in observed mortality rates almost disappeared after censoring at 5 years of follow-up (Table 1).

Absolute excess mortality rate for all-causes of death

Figure 1 demonstrates that adult patients on RRT had a decrease in the absolute all-cause excess mortality rate from 136 extra deaths per 1,000 person-years in 2007 to 116 extra deaths per 1,000 person-years in 2015. In dialysis patients, the excess mortality rate decreased from 165 extra deaths per 1,000 person-years to 148 extra deaths per 1,000 person-years, whereas in patients with a functioning kidney transplant the excess mortality was low and constant at approximately 7 extra deaths per 1,000 person-years. Excess mortality rates were about 20 times higher in patients on dialysis compared with transplanted patients, but with decreasing mortality in dialysis patients this ratio decreased slightly over time (Figure 1). In patients on hemodialysis (HD) between 2007 and 2015 the excess mortality rate decreased from 178 extra deaths per 1,000 person-years to 154 extra deaths per 1,000 person-years, whereas in patients on peritoneal dialysis (PD) it fluctuated around 108 extra deaths per 1,000 person-years (Figure S1). For transplant recipients the excess mortality rate was stable over time at approximately 9 extra deaths per 1,000 person-years for deceased donor transplants and 3 extra deaths per 1,000 person-years for living donor transplants (data not shown).

Table S1 shows the observed and expected numbers of deaths, and crude observed and excess mortality rates by age and calendar year. Figure 2 shows the age-stratified absolute excess mortality rates for all patients on RRT, and for patients on dialysis and with a functioning kidney transplant. The highest excess mortality rates were observed among the oldest patients. In patients on RRT, the strongest decrease in excess mortality rate was observed in patients aged 65 years and older, with more modest reduction in younger patients. In patients on dialysis, the excess mortality rate mainly decreased in older patients, while in transplant recipients it remained similar over time in all age groups. To enable comparison with the results from the US[5], Figure S2 shows the age-stratified absolute excess mortality rates for RRT patients using the age categories 25-44, 45-64 and 65 and over.

Absolute excess mortality rate for specific causes of death

Table S2 displays the different categories of causes of death. For the analyses by cause of death, data from 186,371 patients (66.5% of total) was included. In patients on RRT, the highest excess mortality rate was found for non-atheromatous cardiovascular diseases (CVD) and the lowest rate for malignancies, whereas over time the largest decrease was observed for atheromatous CVD (Figure 3). In dialysis patients the highest excess mortality rate was observed for non-atheromatous CVD (Figure 3), this was the case for both HD and PD patients (Figure S3). In the total group of dialysis patients, all cause-specific excess mortality rates decreased over time, particularly for atheromatous CVD. This was also true for HD patients, whereas PD patients showed a downward trend for atheromatous CVD, no change for infections, and an upward trend for non-atheromatous CVD. In kidney transplant recipients the highest excess mortality rate was observed for infections (Figure 3). Nevertheless, the cause-specific excess mortality rates seemed to be low and stable over time.

Relative excess mortality risk for all-causes of death

Table 2 shows the unadjusted and adjusted all-cause relative excess mortality risk (RER) in the total adult RRT population, as well as stratified by age and RRT modality. The unadjusted and adjusted results were similar. The adjusted RER in patients on RRT was 0.84, 95% confidence interval (CI) 0.83-0.84), implying that the excess mortality risk decreased by 16% for any 5-year interval between 2002 and 2015. We observed a similar decrease in excess mortality risk in males and females on RRT, RER 0.84 (95%CI 0.83-0.85) and 0.83 (95%CI 0.82-0.84), respectively. Although the excess mortality risk in RRT patients decreased within all age groups, the magnitude of the reduction differed, with the greatest relative decrease in patients aged 20-44 years ($p<0.001$). In addition, small variations in RER were observed between the different countries participating in this study ($p<0.001$), however, all countries showed a decreasing trend (data not shown).

The trend in excess mortality risk also differed by RRT modality ($p<0.001$). In patients on dialysis the excess mortality risk decreased by 14% (RER 0.86; 95%CI 0.85-0.86) per 5 years, whereas it increased by 16% (RER 1.16; 95%CI 1.07-1.26) per 5 years in kidney transplant recipients (Table 2). For transplant recipients with a deceased donor transplant the excess mortality risk increased by 18% (1.18; 95%CI 1.08-1.30). In patients with a living donor transplant the number of deaths was too small to perform any further analyses.

Dialysis patients showed a decrease in excess mortality risk in all age groups, ranging from 9% for patients aged 20-44 years to 16% for patients aged 75 years and above. Similar trends were found for HD patients, whereas in PD patients both the overall excess mortality risk as well as the age-specific excess mortality risk remained stable over time (Table 2). In kidney transplant recipients the excess mortality risk remained stable for patients younger than 65 years but increased with 47% per five years for patients aged 65 years and older (Table 2). In a sensitivity analysis, including the date of first transplantation as starting point in transplant recipients, the excess mortality risk increased with 7% (RER 1.07; 95%CI 1.00-1.15) instead of 16% per five years. In patients aged 65 years and older, the excess mortality risk increased with 38% (RER 1.38; 95%CI 1.22-1.57) instead of 47%.

Similar trends were observed before and from 2010 onwards (Table S3). The reduction in excess mortality risk in patients on RRT and the subgroup on dialysis became less prominent after 2010, while the increase in excess mortality risk in transplant recipients became stronger and only reached statistical significance after 2010.

Relative excess mortality risk for specific causes of death

Table 3 shows that between 2002 and 2015 there was a decrease in the cause-specific excess mortality risk in adult RRT patients of 29% per five years for atheromatous CVD, 11% for non-atheromatous CVD, 12% for infections, and 6% for malignancies. Across all age groups, the excess mortality risk declined over time for virtually all causes of death, although there was more uncertainty for malignancies in all age groups, and infections in the youngest age group than for others (Table S4).

In dialysis patients, the excess mortality risk decreased over time for all causes of death, with the largest decrease for atheromatous CVD (Table 3). Also, HD patients showed a decrease in excess mortality risk for all causes of death, whereas in PD patients the risk decreased for atheromatous CVD and increased for non-atheromatous CVD (Table 3). In dialysis patients younger and older than 65 years, the strongest decrease in excess mortality risk was found for atheromatous CVD, whereas no statistically significant effect was found for malignancies in both age groups (Table S5). In kidney transplant recipients, the excess mortality risk remained stable for atheromatous CVD, non-atheromatous CVD and infections, while for malignancies a 2.51 fold increase was observed (Table 3).

Discussion

Among 280,075 adult European patients starting RRT between 2002 and 2015, the all-cause excess mortality relative to the general population decreased with advancing calendar year in all age groups, suggesting that enhanced survival observed in patients on RRT is not only due to the better survival in the general population, but also due to an additional improvement in survival of the RRT population.

Although the same methods were applied in the current study as Foster et al. used in a study carried out in the US,[5] we found lower excess mortality rates for RRT patients in Europe. For example, in RRT patients aged 65 years and older, we observed an excess mortality rate of 206 extra deaths per 1,000 person-years in 2007 compared with 241 extra deaths per 1,000 person-years in the US (Figure S2).[5] This difference may be due to differences in referral patterns, patient population and clinical practice.[13-15] For example, the proportion of diabetes and hypertension as primary kidney disease is higher among RRT patients in the US, whereas the proportion of RRT patients with glomerulonephritis is higher in Europe.[5] As the US had a higher excess mortality rate, changes in the number and severity of comorbidities may have had a larger effect in the US RRT population because there was more room for improvement. Nonetheless, trends in all-cause excess mortality for RRT patients in Europe were similar to those in the US.[5] Both our study and the one by Foster et al. showed that within the youngest age group the greatest relative benefit over time was experienced as the relative excess mortality risk for this age group decreased most. However, from the perspective of deaths prevented, the older patients on RRT showed the best results. Although the relative excess mortality risk within the older age groups decreased less than in the youngest age group, the absolute excess mortality rate was many times higher, resulting in a much more prominent decrease in absolute excess mortality rates over time in older than in younger patients on RRT.

We observed a stronger decrease in excess mortality risk for the total RRT population than in the dialysis population. This may be explained by a higher percentage of RRT patients receiving a kidney transplant over time. The mortality rate in kidney transplant recipients was lower than in dialysis patients. With more patients receiving a transplant over time, the total RRT excess mortality may decline more rapidly than that in the dialysis population.

Trends in dialysis patients

The observed decrease in absolute excess mortality rate in RRT patients was mainly due to the reduced rate in HD patients. Changes in clinical practice and uptake of clinical guidelines may have contributed to the improved survival of HD patients.[16-18] Work by Tentori et al. showed that over time most European countries included in the Dialysis Outcomes and Practice Patterns Study (DOPPS) had a longer HD session time, which was associated with a lower mortality risk.[19,20] Additionally, a decrease in interdialytic weight gain, as shown from phase 2 to 5 in the DOPPS study, may have led to a reduction in intradialytic hypotensive episodes, thereby contributing to the enhanced survival.[21]

The lack of improvement of the excess mortality risk in PD patients may be due to the lower excess mortality rates, leaving less room for improvement over time. In addition, the time on PD before switching to another modality is relatively short for most PD patients. As a consequence, PD mortality primarily reflects short-term mortality, while in HD patients the follow-up is usually substantially longer, which may explain the greater survival improvement over time.

In our cause-specific analyses, we observed the highest excess mortality rate in dialysis patients for CVD and infections and the lowest rates for malignancies, which is in line with previous studies on cause-specific mortality in dialysis patients.[22,23] Both HD and PD patients showed a decrease in excess mortality for atheromatous CVD, and previous studies in Europe, the US, Australia and New-Zealand have also observed a decrease in cardiovascular mortality in dialysis patients over time.[4,24-26] The fact that especially the number of deaths due to atheromatous CVD is decreasing over the last decades might be considered surprising when taking into account the negative randomized controlled trials in dialysis patients.[27-30] However, due to the multifactorial nature of excess cardiovascular mortality in this patient group, the observed decrease may be explained by multiple changes instead of one single intervention. Ceretta et al.[31] showed that in Europe between 2005 and 2014, the percentage of patients with ischemic heart disease as a comorbidity at the start of RRT decreased indicating that patients start dialysis in better cardiovascular health, which may have contributed to the improved survival observed in this study. Furthermore, better management of dialysis patients with myocardial infarction or stroke in the last decades may partly explain the decrease in excess atheromatous CVD mortality. In addition, the implementation of the KDIGO clinical practice guideline on chronic kidney disease-mineral and bone disorder in 2009 led to a higher awareness of disturbances in calcium and phosphorus metabolism.[32] As a consequence, vascular calcification in dialysis patients might be delayed or even prevented.[33,34]

Although less prominent than for mortality due to atheromatous CVD, also a decrease in excess mortality due to infections was observed in patients on HD. This may be the consequence of better prevention of infections in HD patients.[35-37]

Trends in patients with a functioning kidney transplant

We observed a very low excess mortality rate of 7 extra deaths per 1,000 person-years in patients with a functioning kidney transplant when compared to the general population. However, in contrast to the study by Foster et al.,[5] we found a statistically significant increase in excess mortality risk, particularly in older patients. Even after correcting for the increase in kidney transplantation rate over time by including the date of transplantation as starting point in the RER models, we still observed an increase in excess mortality risk for transplant recipients. It should be noted that due to the low excess mortality rate in transplant patients, small changes in the absolute mortality rate may have resulted in a large effect on the RER. Moreover, during our study period the mortality rate in the general population decreased, whereas the mortality rate in kidney transplant patients remained stable or slightly increased, contributing to an increase in excess mortality. The lack of improvement of the mortality rate in transplant patients may be explained by the increased acceptance of older patients for kidney transplantation,[38] as well as by greater acceptance of older and marginal kidney donors.[39]

In kidney transplant recipients, the excess mortality remained stable over time for nearly all specific causes of death. However, we did observe an increase in excess mortality risk for malignancies. In our all-cause sensitivity analyses, we observed that the increased RER in transplant recipients became stronger and only reached statistical significance after 2010. Given that cause-specific excess mortality risk for infections and malignancies either did not change or worsened, we hypothesize that higher burden of immunosuppression among the transplant recipients in more recent years may have reduced the rejection rates, but at the expense of a greater risk of infections and malignancies. However, we could not find any confirmation of this notion in the literature. In addition, as mentioned previously, small changes in the absolute mortality rates may have a large relative effect if the excess mortality rates are low. The absolute excess mortality rates for malignancies fluctuated around zero, with negative excess mortality rates of approximately -0.4 per 1000 person-years before 2012 and positive rates after 2012 (around 0.4 per 1000 person-years), resulting in a significant increase in excess mortality risk. This finding suggests that the observed increase in excess mortality due to malignancies in kidney transplant recipients is the result of declining mortality rates in the general population.[11]

Strengths and limitations

The main strength of this study is the inclusion of a large cohort of over 280,000 patients on RRT from 12 European countries, over a 14 year time period. Another strength is the use of RRT modality-specific analyses per calendar year as patients may have switched from one modality to another. A limitation of our study is that we were not able to include patients from Eastern European countries. Therefore, the results may not be generalizable to the whole of Europe. Furthermore, the study is limited by the lack of information on patient characteristics such as comorbidities, ethnicity, socioeconomic status, medication use, and patient GFR at the start of RRT and additional dialysis and transplantation characteristics such as the type of vascular access and KDPI. Another strength of our study was the ability to investigate cause-specific excess mortality. However, we were only able to include broad categories of causes of death with different data sources for the general population and the patient population. This may have led to some misclassification. A group featuring the other causes of death was added to the analyses in order to demonstrate that the other causes of death showed similar trends over time compared with the cause of death groups included in this study. Finally, not all countries included in this study provided cause of death data, reducing the power in our cause-specific excess mortality analyses; nonetheless 186,371 patients (66.5%) were included in these analyses.

Conclusion

Our study showed that between 2002 and 2015 the excess mortality decreased among patients on RRT in Europe, showing that the better survival observed in patients on RRT is not only due to the enhanced survival in the general population, but also due to an additional improved survival in the RRT population. In dialysis patients, especially on HD, the excess mortality decreased over time, which was predominantly the result of a decrease in atheromatous CVD as cause of death. Excess mortality due to non-atheromatous CVD and infections decreased to a lesser extent and future studies may focus on strategies to further reduce excess mortality due to these causes. Although the excess mortality risk increased over time in kidney transplant recipients, the absolute excess mortality rate was low, confirming that kidney transplantation is the best treatment option for most patients with ESKD.

Methods

RRT population

The ERA-EDTA Registry collects individual patient data from national and regional renal registries in Europe that have data available on both dialysis and kidney transplant patients. Participating national and regional renal registries yearly provide a dataset to the ERA-EDTA Registry, containing at least the month and year of birth, sex, primary kidney disease, date of RRT onset, treatment modality at baseline and during follow-up, and date and cause of death of the patients in their coverage area. Details of the methods used for data collection and data processing can be found in the ERA-EDTA Registry Annual Report.[1] Only data from registries with a full coverage of their country or region during the entire study period of 2002 to 2015 were included in the analyses. The study cohort consisted of patients aged 20 years and older who started RRT between 1 January 2002 and 31 December 2015 in 12 European countries, from 9 national renal registries (Austria, Denmark, Finland, France (regions Auvergne, Limousin, Lorraine, Rhône-Alpes, together covering 16.5% of France), Greece, Iceland, the Netherlands, Norway and Sweden) and 12 regional renal registries (Dutch- and French-speaking Belgium, the Spanish regions of Andalusia, Aragon, Asturias, Basque country, Catalonia, Cantabria, Castile and Leon, and Valencia (together covering 61.4% of Spain), and UK England, Wales, and Scotland). In total, the registries contributing data to this study covered 119 million Europeans, comprising approximately 47.5% of the Northwestern European population and 30.6% of the Southern European population. In line with the study of Foster et al., patients who died on the date of first RRT (N=100, 0.04%) were excluded from the analyses and patients who received a third kidney transplant (N=111, 0.16%) were censored at the date of that transplantation.[5]

General population

Mortality data from the general population of the countries included in this study were obtained from the World Health Organization (WHO) and were used to calculate the mortality rates. The WHO provides mortality data (as number of deaths) coded according to the International Statistical Classification of Diseases and Related Health Problems (ICD) stratified by country, 5-year age group, sex, and calendar year. For each country, the number of deaths for each cause of death were obtained between 2002 and 2015, using ICD-9 or ICD-10 codes (Table S2).[40,41]

Primary exposure and outcome variables

The primary exposure was the calendar year of observation (time-varying, continuous variable). The primary outcome was all-cause excess mortality in patients on RRT. Furthermore, different groups were made for the cause specific excess mortality analyses, including CVD, infections and malignancies. CVD was subdivided into atheromatous CVD (myocardial ischemia and infarction, cerebrovascular diseases and mesenteric infarction) and non-atheromatous CVD (all other cardiovascular diseases), using the ICD-9 or ICD-10 codes for the general population and the ERA-EDTA Registry cause of death codes for the RRT patients (Table S2).[1,40] Patients from the Spanish regions Castile and Leon and Valencia, and those from UK England and Wales as well as France were excluded from the cause-specific mortality analyses since for these countries and regions the cause of death was either not reported or was missing in more than 25% of cases.

Data structure

The SAS macro Lexis was used to split each patient's observation into multiple intervals based on calendar year.[42,43] Time zero was the date of first RRT. Patients were censored at the end of the study period (31 December 2015). For each patient, the current age and RRT modality (HD, PD or kidney transplantation) were determined for each calendar year based on the age and modality at the first of July, leading to a dynamic dataset as patients were followed over time.

Absolute excess mortality rate

Absolute excess mortality rate (deaths per 1,000 person-years) for each age interval in each calendar year was defined as the observed number of deaths in the RRT population minus the expected number of deaths (based on the mortality rate in the general population), divided by the number of RRT person-years, multiplied by 1,000. The expected number of deaths was calculated as the five-year age-, sex-, and calendar year–specific mortality rates in the general population multiplied by the number of RRT person-years within the same age-, sex- and calendar year.

During the study period, in Europe, the proportion of incident and prevalent patients on RRT changed over time, with an increasing percentage of prevalent patients on RRT. This may result in a 'healthier' cohort in the more recent calendar years, since the most severely ill patients will have died in the first years after initiating RRT. To maintain a stable proportion of incident and prevalent RRT patients in the absolute excess mortality rate analyses, patients on RRT were censored after 5 years of follow-up. As a result, the proportion of incident and prevalent RRT patients became stable from 2007 onwards, hence, the absolute excess mortality rate figures start from this year.

Relative excess mortality risk

Time-dependent relative survival models with time-varying covariates were used to estimate the RER in RRT patients associated with advancing calendar year. Relative survival models assume constant hazards in each interval, which implies a Poisson process for the number of deaths in each interval.[44,45] We assumed a constant hazard within each 1-year interval. The SAS procedure GENMOD (with a Poisson error structure) was used to generate generalized linear models.[5,43]

RER models were made for all RRT patients and an interaction term between RRT modality and calendar year was used to obtain model estimates separately for dialysis patients and kidney transplant recipients. Unadjusted models included current age, current calendar year, and follow-up year, whereas adjusted models further included sex, primary kidney disease, and country. One of the advantages of the RER models is that they account for patient-specific follow-up year by including this as a factor in the models. As a consequence, complete follow-up data could be used for these analyses, and therefore, patients were not censored after 5 years of follow-up in the RER analyses. To determine whether changes in excess mortality risk over time differed by age, the age group-specific models included an interaction between current age group (20–44, 45–64, 65-74 and ≥75 years) and calendar year. For the change in excess mortality risk in different age groups in the modality-specific models, an interaction term for time-varying RRT modality, by age group, and by calendar year was added. Finally, RER models were made with an interaction term between dialysis modality and transplant type and calendar year to obtain model estimates for HD or PD patients and for kidney transplant recipients with a graft from a living or deceased donor separately. Although the models provided RER estimates for a 1-year interval in calendar year, these were scaled up to the fifth power to obtain RER estimates for a 5-year interval in calendar year.

Sensitivity analyses were performed to investigate whether a country or study period had an effect on the trends in excess mortality. In addition, to investigate the influence of the increased kidney transplantation rate over time, a sensitivity analysis was performed using the date of first transplantation as the starting point in the RER models. All analyses were performed using SAS software version 9.4.[46]

Disclosure

No conflicts of interest were declared.

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Tables and figures

Table 1. Patient characteristics by calendar period and age group among European adults who initiated RRT between 2002 and 2015.

	Total	Calendar year				Age group (years)			
Total study population		2002-2006	2007-2009	2010-2012	2013-2015	20-44	45-64	65-74	75+
Person-years									
On RRT	1,031,390	168,728	223,459	290,777	348,427	154,586	364,567	251,433	260,804
On dialysis, all modalities (%)	729,654 (70.7)	146,942 (87.1)	169,874 (76.0)	197,844 (68.0)	214,994 (61.7)	69129 (44.7)	214160 (58.7)	196068 (78.0)	250296 (96.0)
With a functioning kidney transplant (%)	301,422 (29.2)	21,648 (12.8)	53,499 (23.9)	92,867 (31.9)	133,408 (38.3)	85367 (55.2)	150228 (41.2)	55335 (22.0)	10492 (4.0)
Age (%)									
20-44 years		15,1	15,4	15,2	14,5				
45-64 years		33,5	34,8	35,8	36,2				
65-74 years		26,6	24,2	23,4	24,2				
75[+] years		24,8	25,6	25,6	25,0				
Sex (%)									
Female	37.5	38.5	37.7	37.4	37.0	38.2	36.9	36.5	38,9
Male	62.5	61.5	62.3	62.6	63.0	61.8	63.1	63.5	61,1
Primary kidney disease (%)									
Diabetes mellitus	21.0	22.1	21.6	20.8	20.2	15.2	22.4	25.3	18.3
Renal vascular disease	3.9	4.6	4.4	3.9	3.2	0.6	1.8	4.8	7.8
Hypertension	11.4	11.6	11.4	11.3	11.3	5.7	8.3	12.2	18.2
Polycystic kidney disease	8.8	7.5	8.4	9.0	9.6	5.3	14.9	7.4	3.4
Glomerulonephritis/sclerosis	15.8	14.5	15.5	16.0	16.4	26.9	18.5	12.6	8.4
Pyelonephritis	6.7	6.9	6.9	6.6	6.5	10.8	5.8	5.7	6.4
Other	15.2	15.2	14.8	15.1	15.5	19.8	14.1	15.2	13.9
Unknown	16.4	16.9	16.5	16.5	16.1	14.6	12.9	16.0	22.8
Missing	0.9	0.8	0.6	0.7	1.2	1.1	1.0	0.8	0.6
Number of deaths									
All RRT	143,778	30,241	33,362	38,236	41,939	3,317	25,456	39,859	75,146
Dialysis, all modalities	138,213	29,986	32,555	36,565	39,107	2,921	23,285	37,692	74,315

Kidney transplant	5,556	250	804	1,670	2,832	396	2,167	2,166	827
Observed absolute mortality rate per 1,000 person-years (95%CI)									
All RRT	139	179	149	131	120	21	70	159	288
	(139-140)	(177-181)	(148-151)	(130-133)	(119-122)	(21-22)	(69-71)	(157-160)	(286-290)
Dialysis, all modalities	189	204	192	185	182	42	109	192	297
	(188-190)	(202-206)	(190-194)	(183-187)	(180-184)	(41-44)	(107-110)	(190-194)	(295-299)
Kidney transplant	18	12	15	18	21	5	14	39	79
	(18-19)	(10-13)	(14-16)	(17-19)	(20-22)	(4-5)	(14-15)	(37-41)	(73-84)
Censored study population									
Person-years									
On RRT	770,045	168,728	191,076	201,122	209,119	108,418	258,091	192,915	210,621
On dialysis, all modalities (%)	621,932	146,942	154,186	159,329	161,475	60,196	185,286	169,056	207,394
	(80.8)	(87.1)	(80.7)	(79.2)	(77.2)	(55.5)	(71.8)	(87.6)	(98.5)
With a functioning kidney transplant (%)	147,810	21,648	36,805	41,732	47,625	48,139	72,630	23,830	3,211
	(19.2)	(12.8)	(19.3)	(20.7)	(22.8)	(44.4)	(28.1)	(12.4)	(1.5)
Number of deaths									
All RRT	118,272	30,241	29,806	29,165	29,060	2,701	20,636	33,099	61,836
Dialysis, all modalities	116,340	29,986	29,310	28,636	28,408	2,511	19,765	32,393	61,671
Kidney transplant	1,923	250	493	528	652	190	867	705	161
Observed absolute mortality rate per 1,000 person-years (95%CI)									
All RRT	154	179	156	145	139	25	80	172	294
	(153-154)	(177-181)	(154-158)	(143-147)	(137-141)	(24-26)	(79-81)	(170-173)	(291-296)
Dialysis, all modalities	187	204	190	180	176	42	107	192	297
	(186-188)	(202-206)	(188-192)	(178-182)	(174-178)	(40-43)	(105-108)	(190-194)	(295-300)
Kidney transplant	13	12	13	13	14	4	12	30	50
	(12-14)	(10-13)	(12-15)	(12-14)	(13-15)	(3-5)	(11-13)	(27-32)	(42-58)

The characteristics are given in person-years and as percentage of person-years. RRT, renal replacement therapy; CI, confidence interval.

Figure 1. Absolute excess mortality rate in European adults who initiated RRT between 2002 and 2015, overall and by RRT modality. Patients were censored after 5 years of follow-up, resulting in 770,045 person-years (PY) on RRT, of which 621,932 PY were spent on dialysis and 147,810 PY with a functioning kidney transplant. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards. RRT, renal replacement therapy.

Figure 2. Absolute all-cause excess mortality rate in European adults who initiated RRT between 2002 and 2015 by age group. Patients were censored after 5 years of follow-up, resulting in 770,045 person-years (PY) on RRT (left panel), of which 621,932 PY were spent on dialysis (middle panel) and 147,810 PY with a functioning kidney transplant (right panel). Please, note the different scale on Y-axis. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards. Due to the small number of patients with a functioning kidney transplant in the different age groups, the yearly estimates show a larger fluctuation. RRT, renal replacement therapy.

Figure 3. Absolute cause-specific excess mortality rate in European adults who initiated RRT between 2002 and 2015. In total, 186,110 patients on RRT were included. After censoring these patients at 5 years of follow-up, they contributed to the study with 504,845 person-years (PY) on RRT (left panel), of which 410,603 PY were spent on dialysis (middle panel) and 94,214 PY with a functioning kidney transplant (right panel). Please, note the different scale on Y-axis. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards. Due to the small number of patients with a functioning kidney transplant in the different cause of death groups, the yearly estimates show a larger fluctuation. RRT, renal replacement therapy.

Table 2. Relative all-cause excess mortality risk per 5-year interval in calendar year for European adults who initiated RRT between 2002 and 2015, by RRT modality and age category.

	Unadjusted RER[a] (95% CI)	**Adjusted RER[b] (95% CI)**
RRT		
All adults	0.84 (0.84 to 0.85)	0.84 (0.83 to 0.84)
20-44 years	0.79 (0.75 to 0.83)	0.76 (0.72 to 0.80)
45-64 years	0.80 (0.79 to 0.82)	0.80 (0.78 to 0.81)
65-74 years	0.83 (0.82 to 0.85)	0.84 (0.82 to 0.85)
75+ years	0.90 (0.89 to 0.91)	0.89 (0.87 to 0.90)
Dialysis, all modalities[c]		
All adults	0.86 (0.86 to 0.87)	0.86 (0.85 to 0.86)
20-44 years	0.93 (0.88 to 0.98)	0.91 (0.87 to 0.96)
45-64 years	0.92 (0.90 to 0.93)	0.90 (0.89 to 0.92)
65-74 years	0.87 (0.86 to 0.89)	0.86 (0.85 to 0.88)
75+ years	0.85 (0.84 to 0.86)	0.84 (0.83 to 0.86)
Hemodialysis[c]		
All adults	0.84 (0.83 to 0.85)	0.83 (0.82 to 0.84)
20-44 years	0.88 (0.83 to 0.93)	0.85 (0.80 to 0.90)
45-64 years	0.88 (0.86 to 0.90)	0.87 (0.85 to 0.89)
65-74 years	0.85 (0.84 to 0.86)	0.84 (0.82 to 0.85)
75+ years	0.83 (0.82 to 0.85)	0.83 (0.82 to 0.84)
Peritoneal dialysis[c,d]		
All adults	1.01 (0.98 to 1.05)	1.01 (0.98 to 1.04)
20-44 years	1.04 (0.90 to 1.20)	1.04 (0.90 to 1.20)
45-64 years	0.98 (0.92 to 1.04)	0.99 (0.93 to 1.05)
65-74 years	1.01 (0.96 to 1.07)	1.01 (0.96 to 1.07)
75+ years	1.01 (0.95 to 1.06)	1.01 (0.95 to 1.06)
Kidney transplant[c]		
All adults	1.21 (1.11 to 1.32)	1.16 (1.07 to 1.26)
20-44 years[d]	0.95 (0.77 to 1.17)	0.90 (0.73 to 1.11)
45-64 years[d]	1.07 (0.95 to 1.22)	1.01 (0.90 to 1.14)
65+ years[d]	1.53 (1.32 to 1.78)	1.47 (1.27 to 1.70)

In the all-cause excess mortality risk analyses, all 280,075 RRT patients were included with a total follow-up time of 1,031,390 person-years on RRT, of which 729,654 person-years were spent on dialysis and 301,422 person-years with a functioning kidney transplant. The interaction terms for year by age group, year by RRT modality and year by age group by RRT modality were all statistically significant (p=0.001).

[a] Unadjusted models for all adults included follow-up, current age (as continuous variable) and current calendar year. Unadjusted models per age group included follow-up and current calendar year.

[b] Adjusted models further included sex, primary kidney disease and country.

[c] RRT modality was included in the model as an interaction term with current calendar year

[d] Models from 2004 onwards due to the lack of power in the earlier calendar years.

Abbreviations: RRT, renal replacement therapy; RER, relative excess mortality risk.

Table 3. Relative excess mortality risk per 5-year interval in calendar year for European adults who initiated RRT between 2002 and 2015, by RRT modality and cause of death.

Cause of death	Unadjusted RER[a] (95% CI)	Adjusted RER[b] (95% CI)
RRT		
All-causes	0.84 (0.84 to 0.85)	0.84 (0.83 to 0.84)
Atheromatous CVD	0.71 (0.69 to 0.73)	0.71 (0.69 to 0.73)
Non-atheromatous CVD	0.89 (0.87 to 0.91)	0.89 (0.87 to 0.91)
Infections	0.88 (0.86 to 0.90)	0.88 (0.86 to 0.90)
Malignancies	0.99 (0.94 to 1.05)	0.94 (0.89 to 0.99)
Other causes	0.86 (0.84 to 0.88)	0.86 (0.84 to 0.89)
Dialysis, all modalities[c]		
All-causes	0.86 (0.86 to 0.87)	0.86 (0.85 to 0.86)
Atheromatous CVD	0.73 (0.71 to 0.75)	0.72 (0.70 to 0.74)
Non-atheromatous CVD	0.91 (0.89 to 0.93)	0.90 (0.88 to 0.92)
Infections	0.90 (0.88 to 0.92)	0.90 (0.87 to 0.92)
Malignancies	1.00 (0.95 to 1.06)	0.95 (0.90 to 1.00)
Other causes	0.89 (0.86 to 0.91)	0.89 (0.87 to 0.91)
Hemodialysis[c]		
All-causes	0.84 (0.83 to 0.85)	0.83 (0.82 to 0.84)
Atheromatous CVD	0.71 (0.68 to 0.73)	0.70 (0.67 to 0.72)
Non-atheromatous CVD	0.88 (0.86 to 0.90)	0.87 (0.85 to 0.90)
Infections	0.88 (0.86 to 0.90)	0.88 (0.85 to 0.90)
Malignancies	0.99 (0.94 to 1.05)	0.95 (0.90 to 1.00)
Other causes	0.86 (0.84 to 0.89)	0.87 (0.85 to 0.89)
Peritoneal dialysis[c,d]		
All-causes	1.01 (0.98 to 1.05)	1.01 (0.98 to 1.04)
Atheromatous CVD	0.87 (0.79 to 0.95)	0.87 (0.79 to 0.95)
Non-atheromatous CVD	1.12 (1.04 to 1.20)	1.12 (1.04 to 1.20)
Infections	1.00 (0.93 to 1.07)	0.99 (0.92 to 1.07)
Malignancies	0.97 (0.43 to 2.21)	e
Other causes	1.10 (1.00 to 1.20)	1.11 (1.02 to 1.22)
Kidney transplant[c,d]		
All-causes	1.21 (1.11 to 1.32)	1.16 (1.07 to 1.26)
Atheromatous CVD	1.40 (1.00 to 1.98)	1.29 (0.97 to 1.73)
Non-atheromatous CVD	1.03 (0.82 to 1.28)	1.00 (0.80 to 1.23)
Infections	1.01 (0.88 to 1.16)	0.99 (0.86 to 1.14)
Malignancies	2.54 (1.53 to 4.24)	2.51 (1.35 to 4.68)
Other causes	1.25 (0.76 to 2.06)	1.09 (0.74 to 1.61)

186,371 patients on RRT were included with a total follow-up time of 674,980 person-years, of which 480,323 person-years were spent on dialysis and 194,629 person-years with a functioning kidney transplant.

[a] Unadjusted models included follow-up, current age (continuous) and current calendar year.

[b] Adjusted models further included sex, primary kidney disease and country.

[c] RRT modality was included in the model as an interaction term with current calendar year.

[d] Models from 2004 onwards due to the lack of power in the earlier calendar years.

[e] Lack of power, model fit questionable.

Abbreviations: CVD, cardiovascular disease; RRT, renal replacement therapy; RER, relative excess mortality risk.

Supplementary Material

Figure S1. Absolute excess mortality rate in European adults who initiated dialysis between 2002 and 2015, by dialysis modality. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards.

Table S1. Person-years at risk, observed deaths, expected deaths, and absolute excess mortality rates among patients on RRT, by age category and calendar year. Patients were censored after 5 years of follow-up to obtain a stable proportion of incident and prevalent RRT patients from 2007 onwards.

Abbreviations: RRT, renal replacement therapy; PY, person-years.

Figure S2. Absolute excess mortality rate in European adults who initiated RRT between 2002 and 2015, by age group. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards. To enable comparison with the results from Foster et al., CJASN 2018[5], similar age groups are presented (25-44 years, 45-64 years and 65 years and older).

Table S2. Causes of death categories specified by codes from the ERA-EDTA Registry and the ICD-9 and ICD-10 coding systems.

Figure S3. Absolute cause-specific excess mortality rate in European adults who initiated hemodialysis (left panel) or peritoneal dialysis (right panel) between 2002 and 2015. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards.

Table S3. Relative excess mortality risk per 5-year interval in calendar year, by treatment modality and by age category for European adults who initiated RRT before and from 2010.

[a] Unadjusted models for all adults included follow-up, current age (continuous variable) and current calendar year. Unadjusted models per age group included follow-up and current calendar year.
[b] Adjusted models further included sex, primary kidney disease and country.
[c] RRT modality was included in the model as an interaction term with calendar year.
Abbreviations: RRT, renal replacement therapy; RER, relative excess mortality risk

Table S4. Relative excess mortality risk per 5-year interval in calendar year for European adults who initiated RRT between 2002 and 2015, by cause of death and age category.

[a] Unadjusted models for all adults included follow-up, current age (continuous variable) and current calendar year. Unadjusted models per age group included follow-up and current calendar year.
[b] Adjusted models further included sex, primary kidney disease and country.
Abbreviations: RRT, renal replacement therapy; CVD, cardiovascular disease; RER, relative excess mortality risk.

Table S5. Relative excess mortality risk per 5-year interval in calendar year for European adults who initiated dialysis, all modalities, between 2002 and 2015, by cause of death and age category.

Age group models from 2004 onwards due to lack of power in the earlier years. Broader age groups (20-64 years and 65+ years) were included to obtain enough power for the analyses.
[a] Unadjusted models for all adults included follow-up, current age (continuous variable) and current calendar year. Unadjusted models per age group included follow-up and current calendar year.
[b] Adjusted models further included sex, primary kidney disease and country.
[c] Lack of power, model fit questionable.
Abbreviations: CVD, cardiovascular disease; RER, relative excess mortality risk.

Supplementary information is available at Kidney International's website

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Figure 1. Absolute excess mortality rate in European adults who initiated RRT between 2002 and 2015, overall and by RRT modality. Patients were censored after 5 years of follow-up, resulting in 770,045 person-years (PY) on RRT, of which 621,932 PY were spent on dialysis and 147,810 PY with a functioning kidney transplant. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards. RRT, renal replacement therapy.

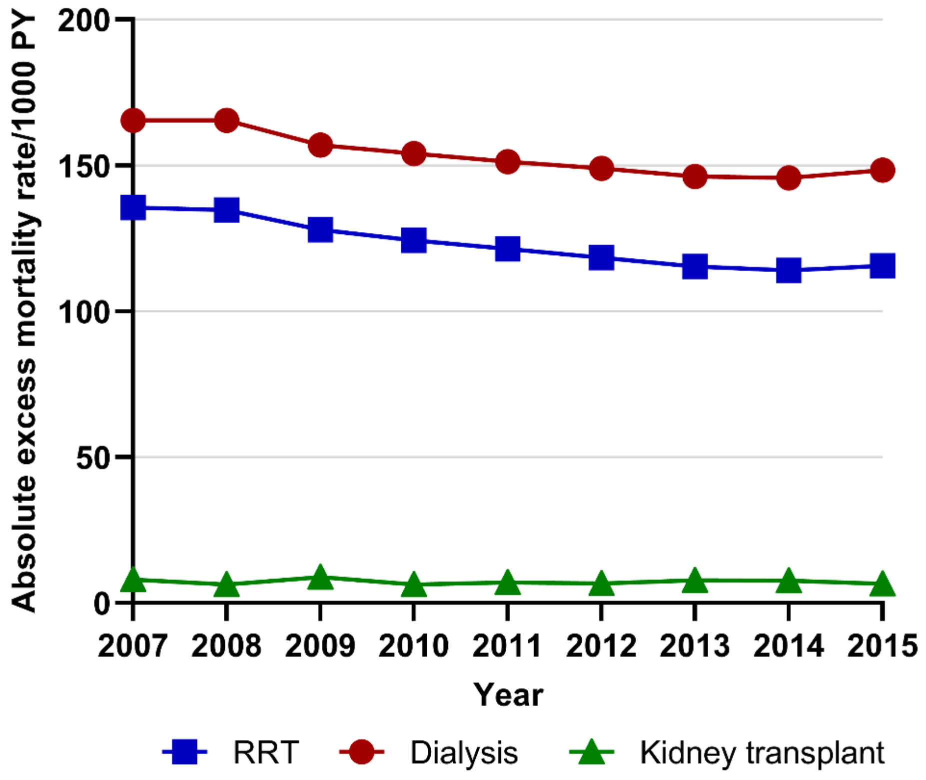

Figure 2. Absolute all-cause excess mortality rate in European adults who initiated RRT between 2002 and 2015 by age group. Patients were censored after 5 years of follow-up, resulting in 770,045 person-years (PY) on RRT (left panel), of which 621,932 PY were spent on dialysis (middle panel) and 147,810 PY with a functioning kidney transplant (right panel). Please, note the different scale on Y-axis. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards. Due to the small number of patients with a functioning kidney transplant in the different age groups, the yearly estimates show a larger fluctuation. RRT, renal replacement therapy.

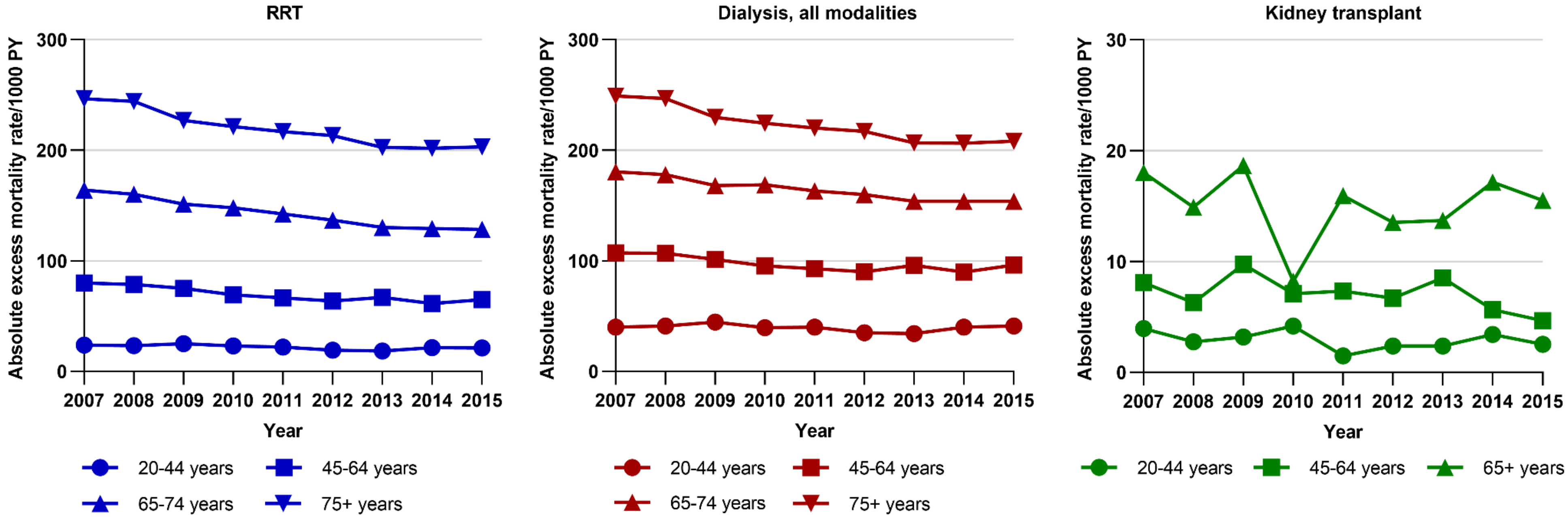

Figure 3. Absolute cause-specific excess mortality rate in European adults who initiated RRT between 2002 and 2015. In total, 186,110 patients on RRT were included. After censoring these patients at 5 years of follow-up, they contributed to the study with 504,845 person-years (PY) on RRT (left panel), of which 410,603 PY were spent on dialysis (middle panel) and 94,214 PY with a functioning kidney transplant (right panel). Please, note the different scale on Y-axis. Censoring the patients' follow-up after 5 year led to a stable proportion of incident and prevalent patients on RRT from 2007; therefore the results are shown from 2007 onwards. Due to the small number of patients with a functioning kidney transplant in the different cause of death groups, the yearly estimates show a larger fluctuation. RRT, renal replacement therapy.