



Incidence and relative risk of renal replacement therapy in people with and without diabetes between 2002 and 2016 in a German region

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Abstract

Aims/hypothesis Data on trends of end-stage renal disease among people with diabetes are lacking. We analysed the incidence of end-stage renal disease, defined as renal replacement therapy, among people with and without diabetes, and the corresponding relative risk. Moreover, we investigated time trends for the period 2002–2016.

Methods In this retrospective population-based study we analysed data from one dialysis centre of a region in Germany covering a population of about 310,000 inhabitants. We estimated the age- and sex-standardised incidence rates for chronic renal replacement therapy among adults with and without diabetes and the corresponding relative risks. The time trend was analysed using Poisson regression models.

Results Between 2002 and 2016, 1107 people (61.2% male; mean age 71.6 years; 48.7% with diabetes) had a first renal replacement therapy. During the study period, the incidence rate in the population with diabetes varied from 93.6 (95% CI 50.4, 136.7) in 2002 to 140.5 (95% CI 80.6, 200.4) in 2016 per 100,000 person-years. In the population without diabetes the incidence rate was substantially lower and reached 17.3 (95% CI 10.9, 23.6) in 2002 and 24.6 (95% CI 17.5, 31.7) in 2009. The relative risk comparing people with and without diabetes was 3.57 (95% CI 3.09, 4.13). No significant change in the incidence rates was found during the observation period, either in the population with or in the population without diabetes, and thus the relative risk also remained constant.

Conclusions/interpretation People with diabetes have a higher risk of needing renal replacement therapy than those without diabetes, a fact that remained constant over a time period of 15 years.

Keywords Diabetes · End-stage renal disease · Epidemiology · Incidence · Renal replacement therapy

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Research in context

What is already known about this subject?

- Individuals with diabetes starting renal replacement therapy (RRT) have poorer survival rates and higher treatment costs compared with people without diabetes
- Only a few population-based studies have investigated the incidence and temporal trends of RRT in the population with diabetes compared with the population without diabetes
- Results concerning time trends in the incidence of RRT in people with and without diabetes are contradictory

What is the key question?

- How did the incidence of RRT in people with and without diabetes in Germany change during the period 2002–2016?

What are the new findings?

- Incidence of RRT remained substantially higher among people with diabetes compared with people without diabetes, with an almost fourfold increased risk
- Incidence of RRT remained constant over the time period of 15 years in people both with and without diabetes
- Men had twice as high a risk of needing RRT compared with women

How might this impact on clinical practice in the foreseeable future?

- These results will be useful for practitioners, epidemiologists and healthcare planners when discussing the quality of diabetes care

Abbreviations

ESRD	End-stage renal disease
IR	Incidence rate
PY	Person-years
RRT	Renal replacement therapy

Introduction

The increasing prevalence of diabetes mellitus worldwide [1] leads to an increase in the number of people with complications of diabetes, including diabetic nephropathy and its last stage, end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). Among people starting RRT, the proportion of individuals with diabetes (as comorbidity) ranges between 28% [2] and 51% [3]. Individuals with diabetes and ESRD have poorer survival rates than people without diabetes [2, 4–6]. Moreover, this group of individuals brings about especially high treatment costs [7, 8]. Nevertheless, there are only a few population-based studies that have analysed the incidence of RRT in the population with diabetes compared with the population without diabetes, in particular where diabetes was taken into account as a comorbidity and not only diabetic nephropathy as a primary kidney disease leading to ESRD [3, 4, 9–11]. In our previous study we analysed the incidence of RRT in 2002–2008 in a German region stratified

by diabetes status [9]. In this study, no temporal change regarding the incidence of RRT could be detected among people either with or without diabetes. However, the considered time period of this study was quite short. Furthermore, a national guideline was implemented in 2010 in Germany addressing treatment and healthcare of adult individuals with diabetes and renal disease [12]. This may have improved diabetes care in this patient group.

The aims of this study were: (1) to analyse the incidence of RRT among individuals with and without diabetes as well as relative risk (RR) and (2) to investigate the corresponding time trends for the period 2002–2016.

Methods

Study design and data assessment The data analysed were sourced from one dialysis centre, which delivers dialysis to all inhabitants in a region in North Rhine-Westphalia, Western Germany (district of Mettmann excluding the cities of Ratingen, Monheim and Langenfeld), covering a population of about 310,000 inhabitants. As there is only this one dialysis centre in the region, it was assumed that nearly all individuals with RRT living in this region are treated there. This study was designed as a retrospective population-based study.

Study population A census-based description of the general population of the study region was obtained from the Federal

Office for Statistics [13]. The population with diabetes was estimated in the adult population based on age- (30–59, 60–69, 70–79, ≥ 80 years) and sex-specific diabetes prevalence from two German nationwide surveys (German Health Interview and Examination Surveys, GNHIES98 and DEGS1) [14–16] performed in 1997–1999 and 2008–2011, respectively. In both surveys, diabetes was defined by intake of glucose-lowering medication, by self-report of physician-diagnosed diabetes or by an HbA_{1c} value above 47.5 mmol/mol (6.5%) within the last week before the survey [17]. These two surveys are believed to be the only nationwide data sources with a comparable study design that allow the estimation of age- and sex-specific diabetes prevalence, including undetected diabetes, over more than a decade. Since both surveys were truncated at the age of 80 years, and given findings of previous studies [14], we assumed that diabetes prevalence remained constant among people above 80 years. For the main analysis we assumed that the estimated age- and sex-specific diabetes prevalence increased linearly from 2002 to 2011 and also continued to do so thereafter until 2016. Nevertheless, we repeated the main analysis with constant age- and sex-specific diabetes prevalence during the years 2011–2016 in the sensitivity analysis.

Assessment of people with incident RRT and data assessment

In the present analysis, we examined all people aged at least 30 years at the time of first RRT between January 2002 and December 2016. According to our previous study [9], an incident RRT was defined as the first dialysis or primary kidney or combined pancreas-kidney transplantation due to chronic kidney disease. Individuals with RRT due to typical acute kidney insufficiency due to sepsis and other agents were excluded, as were individuals with transplant failure and individuals from outside of the study region.

Demographic data such as age and sex were available for all people with a first RRT. A person was classified as having diabetes according to a history of diabetes, use of a glucose-lowering agent or having HbA_{1c} ≥ 47.5 mmol/mol (6.5%) at the start of RRT [18]. Likewise, the reason for RRT was determined according to established classifications [19–21]. Diabetic nephropathy as a reason for RRT was assumed when an individual had macroalbuminuria or microalbuminuria and diabetic retinopathy, both in the absence of another disease associated with ESRD [22]. Additionally, the type of RRT was documented (i.e. peritoneal dialysis or haemodialysis).

Furthermore, several clinical variables such as GFR (using the Modification of Diet in Renal Disease [MDRD] formula or the Chronic Kidney Disease Epidemiology Collaboration formula [CKD-Epi]), HbA_{1c} value, initial form of RRT, start of dialysis in the clinic (yes vs no), BMI, information regarding type of diabetes and diabetes duration were ascertained.

Moreover, information was obtained regarding the following comorbidities at the start of RRT: hypertension, CHD,

congestive heart failure, myocardial infarction, peripheral artery occlusive disease, amputation, stroke, malignant tumour and presence of diabetic retinopathy among individuals with diabetes only.

Statistical analysis We performed analyses for the population as a whole and separately for men and women. We estimated the number of people with diabetes by multiplying the study population with the estimated diabetes prevalence in each stratum, defined by sex and age (30–59, 60–69, 70–79, ≥ 80 years). Person-years (PY) were calculated by taking the estimated number of people with and without diabetes for each calendar year. We computed stratum-specific and age- and sex-standardised incidence rates (IRs) of RRT with 95% CIs in the estimated population with and without diabetes for each calendar year, using the German population of 2009 as the standard population. Moreover, we estimated the IR ratio by comparing the population with and without diabetes from the standardised IRs. Furthermore, we computed attributable risk among the population with diabetes and population attributable risk due to diabetes along with 95% CIs in order to describe what proportion of RRT could theoretically be avoided if the exposure (i.e. diabetes) was omitted. Time trends were investigated by first fitting separate Poisson regression models with IR of RRT as the dependent variable for individuals with and without diabetes. Age and year of RRT as linear continuous difference from baseline year 2002 were used as the independent variables. The lowest age group (30–59 years) was used as a reference group. Moreover, we fitted analogous Poisson models for the entire population. The variable ‘presence of diabetes’ (yes vs no) and an interaction term for diabetes and years since 2002 were also included.

Furthermore, we estimated IRs and trends of RRT due only to diabetic nephropathy in the diabetic population.

In order to take over-dispersion of the outcome variable into account, all analyses were conducted with the de-scale adjustment based on cumulated data on the covariate strata. The analysis was computed using the statistical analysis system, SAS (SAS for Windows 7, Release 9.4 TS1M1, SAS Institute, Cary, NC, USA).

Ethics All participants were asked to provide their written, informed consent for participation when they started RRT. Individuals who declined (less than 1% of all participants) were excluded from the analysis. The study was approved by the local ethics committee.

Results

Study population The data covered the population aged at least 30 years in the study region (2002: 219,046, 2016: 213,120). Diabetes prevalence in this region increased among

men from 11.8% in 2002 to 13.7% in 2016 but remained nearly constant among women (2002: 11.4%, 2016: 11.4%).

There were 1107 people with a first RRT between 2002 and 2016. The baseline characteristics of these people regarding age, sex, clinical variables and comorbidities are shown in Table 1. The majority of the people starting RRT were men (61.2%). The age distribution of people with RRT was similar among people with and without diabetes, with a mean age of 71.6 years at the time of the first RRT. Nevertheless, the mean age increased significantly during the study period from 67.4 years in 2002 to 73.1 years in 2016 (p value linear regression: $p < 0.001$), with similar increases among all subgroups.

Almost half of all 1107 individuals were classified as having diabetes, with similar proportions among men and women.

The majority of individuals with diabetes had type 2 diabetes (95.6%) and the mean duration of diabetes at the time of the first RRT was 16.9 years, with similar numbers in both sexes. As expected, the mean HbA_{1c} value was significantly higher among people with diabetes than among those without diabetes (HbA_{1c}: 47.7 mmol/mol [6.5%] vs HbA_{1c}: 36.5 mmol/mol [5.5%], p value t test < 0.001), with similar values in men and women.

In almost half of the people with diabetes, diabetic nephropathy was the reason for RRT (49.1%). Vascular nephropathy (kidney disease due to hypertension and micro- and macrovascular diseases) was the reason for RRT in about one-third (33.8%). In the population without diabetes, the most common reason for RRT was vascular nephropathy (39.8%). The majority of people who started RRT began with haemodialysis (61.5%) followed by peritoneal dialysis (38.5%), with similar numbers in all subgroups, while only one person underwent transplantation as the first RRT.

The majority of dialyses started in the clinic (78.6%), with similar proportions in all subgroups. The GFR value was significantly higher in men with diabetes than in those without (p value = 0.0012). In women, this difference was not significant (p value = 0.427).

People with diabetes had significantly more comorbidities and higher BMI at the time of first RRT than those without diabetes (p values χ^2 test and t test < 0.05 , respectively), with the exception of malignant tumour, where an inverse association was observed (p value < 0.001). The proportion of comorbidities was higher among men for all comorbidities except diabetic retinopathy.

IR, relative and attributable risk The age- and sex-standardised IRs of the first RRT are shown in Table 2 and Fig. 1. There were some fluctuations, which were particularly evident in the population with diabetes. During the observation period, the IR in the population with diabetes ranged from 56.2 per 100,000 PY (95% CI 31.1, 81.4) in 2008 to 140.5 per 100,000 PY (95% CI 80.6, 200.4) in 2016, without sex differences. This rate was substantially lower in the population

without diabetes, with values between 17.2 (95% CI 11.0, 23.4) in 2002 and 29.5 (95% CI 21.5, 37.5) in 2009. The RR comparing the IRs among the populations with diabetes and without diabetes ranged between 2.5 (95% CI 1.4, 4.4) in 2009 and 6.0 (95% CI 3.3, 10.8) in 2004. In people with diabetes, 78% of the RRT incidence was attributable to diabetes. In the entire population, one-third of the RRT incidence was attributable to diabetes. The IR was twice as high among men compared with women in subpopulations both with and without diabetes.

IR relating only to diabetic nephropathy tended to decrease, with the highest value in 2003 (87.4; 95% CI 42.6, 132.1) and the lowest value in 2010 (32.1; 95% CI 9.7, 54.5), and was about twofold higher among men than among women (see electronic supplementary material [ESM] Table 1, ESM Fig. 1).

Analysis of time trend and other covariates The results of the incidence trend from the fully adjusted Poisson models are shown in Table 3. The RRs in the population stratified by diabetes status are presented in models 1a and 1b. During the observation period, no change in the IR was observed in the population with diabetes (RR per calendar year, 1.02; 95% CI 0.99, 1.04) for either sex. Likewise, the IR remained nearly constant in the population without diabetes (RR 1.01; 95% CI 0.99, 1.03) both in men and in women. The IR increased substantially with increasing age, with a particularly strong increase in the population without diabetes.

Taking the entire population in model 2, the IR in the population with diabetes was almost fourfold that of the population without diabetes (RR 3.57; 95% CI 3.09, 4.13), with a higher difference among men (RR 4.14; 95% CI 3.39, 5.06). This pattern was particularly strong in the younger population but also persisted in the oldest age group (RR diabetes vs no diabetes < 60 years, 12.60; 95% CI 9.04, 17.55; 80+ years: 2.04; 95% CI 1.58, 2.62) (data not shown). The interaction diabetes \times calendar year as considered in model 3 was nonsignificant, indicating that the RR between the subpopulations with and without diabetes remained constant in both sexes. Results from the sensitivity analysis assumed that diabetes prevalence remained constant after 2011, meaning that they were similar to those from the main analysis (ESM Tables 2, 3).

When RRT due only to diabetic nephropathy was counted, the IR of RRT significantly decreased in the male population with diabetes (RR per calendar year, 0.96; 95% CI 0.93, 0.997) but not in the female population (RR per calendar year, 0.97; 95% CI 0.93, 1.02) (ESM Table 4).

Discussion

Statement of principal findings This is one of the few studies analysing the incidence of RRT in the population with diabetes compared with the population without diabetes. This study also

Table 1 Description of all people with first RRT and the background population, district of Mettmann, 2002–2016

Characteristic	Total	Men	Women	Diabetes	No diabetes	Men		Women	
						Diabetes	No diabetes	Diabetes	No diabetes
All years combined									
Number of people with RRT	1107	677	430	539	568	326	351	213	217
Mean age ^a (years [SD])	71.6 (11.6)	70.9 (11.2)	72.6 (12.2)	71.6 (10.6)	71.6 (12.5)	70.3 (10.2) ^b	71.5 (12.1)	73.5 (11.0) ^b	71.7 (13.2)
Number of people with RRT									
30–59 years	156	99	57	63	93	46	53	17	40
60–69 years	241	159	82	132	109	91	68	41	41
70–79 years	425	271	154	222	203	132	139	90	64
80 years and older	285	148	137	122	163	57	91	65	72
Year RRT started: 2002									
Number of people with RRT	59	35	24	29	30	17	18	12	12
Mean age ^a (years [SD])	67.4 (11.5)	66.0 (10.4)	69.4 (12.9)	70.1 (9.8)	64.8 (12.5)	68.2 (9.7)	63.9 (10.9)	72.8 (9.6)	66.0 (15.2)
Population at risk	219,046	103,210	115,836	25,319	193,727	12,156	91,054	13,163	102,673
Year RRT started: 2003									
Number of people with RRT	74	46	28	37	37	23	23	14	14
Mean age ^a (years [SD])	70.0 (10.4)	70.7 (10.6)	68.9 (10.2)	67.8 (8.8)	72.2 (11.5)	66.6 (8.1)	74.7 (11.5)	69.8 (10)	68.0 (10.7)
Population at risk	218,491	103,007	115,484	25,348	193,143	12,262	90,745	13,086	102,398
Year RRT started: 2004									
Number of people with RRT	60	34	26	30	30	18	16	12	14
Mean age ^a (years [SD])	69.6 (9.5)	68.7 (8.8)	70.7 (10.3)	69.4 (10.6)	69.8 (8.4)	67.8 (9.1)	69.8 (8.7)	71.8 (12.5)	69.7 >(8.3)
Population at risk	218,151	102,808	115,343	25,479	192,672	12,368	90,440	13,111	102,232
Year RRT started: 2005									
Number of people with RRT	73	43	30	37	36	22	21	15	15
Mean age ^a (years [SD])	69.9 (11.6)	69.6 (11.7)	70.2 (11.7)	68.9 (11.0)	70.9 (12.2)	68.1 (10.5)	71.2 (12.8)	70.0 (12.1)	70.4 (11.7)
Population at risk	217,947	102,815	115,132	25,508	192,439	12,436	90,379	13,072	102,060
Year RRT started: 2006									
Number of people with RRT	67	35	32	35	32	20	15	15	17
Mean age ^a (years [SD])	71.2 (11.2)	70.9 (9.3)	71.6 (13.1)	70.6 (8.8)	71.9 (13.4)	68.8 (8.0)	73.7 (10.3)	73.0 (9.4)	70.3 (15.9)
Population at risk	217,632	102,634	114,998	25,592	192,040	12,535	90,099	13,057	101,941
Year RRT started: 2007									
Number of people with RRT	68	38	30	32	36	17	21	15	15
Mean age ^a (years [SD])	72.7 (11.5)	73.0 (8.6)	72.2 (14.5)	74.1 (8.3)	71.4 (13.7)	71.0 (8.3)	74.6 (8.6)	77.6 (7.0)	66.9 (18.1)
Population at risk	217,160	102,339	114,821	25,709	191,451	12,644	89,695	13,065	101,756
Year RRT started: 2008									
Number of people with RRT	58	39	19	28	30	20	19	8	11
Mean age ^a (years [SD])	71.8 (10.4)	74.1 (8.0)	67.1 (13.2)	73.5 (7.0)	70.2 (12.7)	73.3 (7.9)	74.9 (8.2)	74.1 (4.6)	62.0 (15.2)
Population at risk	216,063	101,818	114,245	25,839	190,224	12,777	89,041	13,062	101,183
Year RRT started: 2009									
Number of people with RRT	80	49	31	28	52	15	34	13	18
Mean age ^a (years [SD])	71.6 (12.5)	69.6 (12.7)	74.7 (11.6)	73.0 (8.9)	70.8 (14.1)	71.3 (9.4)	68.8 (14.0)	74.9 (8.1)	74.6 (13.9)
Population at risk	215,345	101,391	113,954	26,065	189,280	12,950	88,441	13,115	100,839
Year RRT started: 2010									
Number of people with RRT	69	40	29	34	35	20	20	14	15
Mean age ^a (years [SD])	74.1 (9.8)	73.4 (9.6)	75.1 (10.2)	74.9 (9.4)	73.4 (10.3)	73.4 (10.3)	73.5 (9.1)	77.0 (7.7)	73.4 (12.1)
Population at risk	215,392	101,408	113,984	26,351	189,041	13,150	88,258	13,201	100,783
Year RRT started: 2011									
Number of people with RRT	74	44	30	43	31	26	18	17	13
Mean age ^a (years [SD])	73.2 (9.7)	71.3 (9.4)	75.9 (9.7)	72.9 (9.2)	73.6 (10.4)	70.7 (9.0)	72.3 (10.1)	76.3 (8.8)	75.5 (11.1)
Population at risk	211,020	99,046	111,974	25,908	185,112	12,930	86,116	12,978	98,996
Year RRT started: 2012									
Number of people with RRT	87	53	34	46	41	28	25	18	16
Mean age ^a (years [SD])	71.6 (13.1)	68.8 (13.8)	76.0 (11.8)	71.3 (12.2)	71.9 (14.3)	68.4 (12.3)	69.2 (14.5)	75.8 (10.8)	76.1 (13.3)
Population at risk	211,171	99,136	112,035	26,049	185,122	13,083	86,053	12,966	99,069
Year RRT started: 2013									
Number of people with RRT	77	48	29	37	40	22	26	15	14
Mean age ^a (years [SD])	68.9 (13.1)	67.8 (13.1)	73.2 (12.5)	69.0 (12.4)	70.6 (13.8)	68.2 (12.5)	67.4 (13.8)	70.2 (12.5)	76.4 (12.1)
Population at risk	211,319	99,259	112,060	26,128	185,191	13,217	86,042	12,911	99,149
Year RRT started: 2014									
Number of people with RRT	75	48	27	33	42	19	29	14	13
Mean age ^a (years [SD])	72.0 (12.4)	71.9 (12.0)	72.2 (13.2)	72.8 (12.3)	71.4 (12.6)	73.2 (11.1)	71.1 (12.7)	72.2 (14.2)	72.2 (12.7)
Population at risk	211,555	99,405	112,150	26,280	185,275	13,383	86,022	12,897	99,253
Year RRT started: 2015									
Number of people with RRT	90	66	24	41	49	27	39	14	10
Mean age ^a (years [SD])	73.9 (10.5)	74.3 (10.3)	72.5 (11.1)	71.9 (11.0)	75.5 (9.9)	72.4 (10.3)	75.7 (10.3)	70.9 (12.5)	74.9 (8.9)
Population at risk	212,393	99,968	112,425	26,324	186,069	13,517	86,451	12,807	99,618
Year RRT started: 2016									
Number of people with RRT	96	59	37	49	47	32	27	17	20
Mean age ^a (years [SD])	73.1 (13.7)	71.7 (13.5)	75.3 (13.9)	73.3 (13.5)	72.8 (14.0)	72.3 (11.8)	71.0 (15.4)	75.3 (16.4)	75.4 (11.9)
Population at risk	213,120	100,269	112,851	26,622	186,498	13,746	86,523	12,876	99,975
Diabetes duration (years [SD]) (138 missing)	–	–	–	16.9 (11.3)	–	16.9 (11.1)	–	16.9 (11.8)	–
Diabetes type (%) (24 missing)									
Type 1	–	–	–	4.4	–	3.9	–	5	–
Type 2	–	–	–	95.6	–	96.1	–	95.0	–

Table 1 (continued)

Characteristic	Total	Men	Women	Diabetes	No diabetes	Men		Women	
						Diabetes	No diabetes	Diabetes	No diabetes
HbA _{1c} value (mmol/mol [SD]) ^a (295 missing)	42.4 (11.1)	42.3 (10.4)	42.7 (12.2)	47.7 (11.5) ^b	36.5 (7.0) ^b	47.4 (11.0) ^b	36.9 (6.2) ^b	48.2 (12.1) ^b	35.8 (8.1) ^b
HbA _{1c} value (% [SD]) ^a (295 missing)	6.0 (1.0)	6.0 (1.0)	6.1 (1.1)	6.5 (1.0) ^b	5.5 (0.6) ^b	6.5 (1.0) ^b	5.5 (0.6) ^b	6.6 (1.1) ^b	5.4 (0.7) ^b
BMI (kg/m ² [SD]) ^a (202 missing)	27.7 (6.2)	27.7 (6.4)	27.7 (6.0)	29.4 (6.0) ^b	26.2 (6.0) ^b	29.6 (5.9) ^b	26.1 (6.3) ^b	29.1 (6.2) ^b	26.4 (5.5) ^b
Reason for RRT (%) (95 missing)									
Diabetic nephropathy	25.0	24.6	25.6	49.1	0	49.2	0	49.1	0
Vascular nephropathy	36.8	38.3	34.2	33.8	39.8	35.1	41.5	31.7	37.0
Glomerulonephropathy	12.2	10.9	14.3	5.2	19.3	4.4	17.3	6.4	22.8
Other/unknown	26.1	26.2	25.9	11.8	40.9	11.2	41.3	12.9	40.2
Initial treatment (%) (36 missing)									
Transplantation	0.1	0.2	0	0.2	0	0.3	0	0	0
HD	61.5	61.4	61.4	61.6	61.3	61.9	61.3	61.1	61.7
Shunt	36.0	38.5	31.9	37.5	34.5	40.3	36.9	33.2	30.6
Central venous catheter	25.5	22.9	29.5	24.1	26.8	21.6	24.2	27.9	31.1
PD	38.5	38.4	38.6	38.2	38.7	37.8	38.9	38.9	38.3
Start of dialysis in the clinic (%) (82 missing)	78.6	77.9	79.9	79.3	78.0	78.8	77.0	80.1	79.6
GFR value (MDRD: ml/min [SD]) ^{a, c} (158 missing)	15.8 (10.9)	16.4 (10.1)	14.9 (11.9)	17.0 (9.2) ^b	14.7 (12.2) ^b	18.1 (9.8) ^b	14.9 (10.1) ^b	15.4 (8.1)	14.3 (14.8)
GFR value (CKD-Epi: ml min ⁻¹ 1.73 m ⁻² [SD]) ^{a, d} (15 missing)	15.4 (13.8)	17.3 (15.8)	11.5 (6.9)	16.6 (14.2)	14.3 (13.3)	19.0 (16.6)	15.9 (15.1)	12.3 (6.4)	10.8 (7.4)
Congestive heart failure (%) ^a (46 missing)	22.6	24.4	19.9	28.4 ^b	17.0 ^b	29.0	19.9	27.5	12.2
Diabetic retinopathy (%) ^a (45 missing)	15.2	14.0	17.0	30.7	0.0	28.7	0.0	33.8	0.0
Hypertension (%) ^a (41 missing)	89.6	90.0	88.9	93.7 ^b	85.5 ^b	93.1 ^b	87.1 ^b	83.1 ^b	94.7 ^b
CHD (%) ^a (32 missing)	38.1	44.1	28.5	46.5 ^b	29.9 ^b	50.8 ^b	37.9 ^b	40.0 ^b	16.8 ^b
Myocardial infarction (%) ^a (41 missing)	15.6	18.1	11.6	19.4 ^b	11.9 ^b	20.7	15.7	17.3 ^b	5.8 ^b
Peripheral artery occlusive disease (%) ^a (31 missing)	21.8	25.5	15.8	28.3 ^b	15.4 ^b	33.4 ^b	18.1 ^b	20.5 ^b	11.1 ^b
Minor amputation (%) ^a (41 missing)	2.5	3.2	1.5	3.6 ^b	1.5 ^b	4.7 ^b	1.8 ^b	1.9	1.0
Major amputation (%) ^a (41 missing)	2.6	3.4	1.5	4.0 ^b	1.3 ^b	5.6 ^b	1.2 ^b	1.4	1.4
Stroke (%) ^a (32 missing)	16.9	18.1	15.1	19.9 ^b	14.1 ^b	21.0	15.4	18.1	12.0
Malignant tumour (%) ^a (31 missing)	24.3	26.3	21.0	19.5 ^b	28.9 ^b	20.1 ^b	32.3 ^b	18.6	23.4

^a Measured during start of RRT^b Significant differences between people with diabetes and without diabetes (*p* value < 0.05 unpaired *t* test for continuous variables, χ^2 test for categorical variables)^c Before 31 December 2013^d After 1 January 2014

CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration formula; HD, haemodialysis; MDRD, Modification of Diet in Renal Disease formula; PD, peritoneal dialysis

evaluated the trend of the incidence of RRT over a time period of 15 years. As expected, the IRs were substantially higher among people with diabetes, with an almost fourfold-increased IR. Men had twice as high a risk of RRT compared with women. The IRs in subpopulations both with and without diabetes and, thus, the corresponding RRs, mainly remained constant throughout the study period, with consistent results in both sexes.

Discussion of important differences in results A comparison with other studies is very difficult. We found only a few population-based studies analysing age- and sex-standardised IRs among people with and without diabetes.

Furthermore, most of the studies investigating the IR of RRT in the population with diabetes only considered diabetic nephropathy as a primary reason for RRT, and not diabetes as a comorbidity.

The IRs among people with diabetes in the current study were somewhat lower than in the previous study in the same study region [9], which included the years 2002–2008: IR 97.9 (95% CI 86.7, 109.1) vs 167 (95% CI 125, 208) per 100,000 PY. This discrepancy is mainly the result of a different methodological approach regarding the estimation of the diabetic population as a population at risk. In the previous study, diabetes prevalence was estimated using the former

Table 2 Incidence of RRT, district of Mettmann, 2002–2016

Variable	IRs ^a (95% CI) per 100,000 PY			Relative and attributable risks (95% CI)		
	IRt	IRd	IRn	RR	ARE	PAR
All years combined						
Total population	32.8 (30.9, 34.7)	97.9 (86.7, 109.1)	21.8 (20.0, 23.6)	4.5 (3.9, 5.2)	0.78 (0.74, 0.81)	0.34 (0.27, 0.40)
Men	46.9 (43.4, 50.5)	129.5 (111.2, 147.7)	32.9 (29.4, 36.4)	3.9 (3.3, 4.7)	0.75 (0.70, 0.79)	0.30 (0.20, 0.39)
Women	22.3 (20.2, 24.5)	69.9 (56.6, 83.2)	14.1 (12.2, 16.0)	5.0 (3.9, 6.3)	0.80 (0.75, 0.84)	0.37 (0.26, 0.46)
Stratified by year						
2002	28.4 (21.1, 35.8)	93.6 (50.4, 136.7)	17.3 (10.9, 23.6)	5.4 (3.0, 9.8)	0.82 (0.67, 0.90)	0.39 (0.35, 0.43)
2003	36.6 (28.1, 45.1)	109.8 (63.1, 156.5)	25.4 (17.0, 33.7)	4.3 (2.5, 7.4)	0.77 (0.60, 0.87)	0.31 (0.14, 0.44)
2004	27.5 (20.5, 34.6)	103.0 (54.5, 151.5)	17.3 (11.0, 23.6)	6.0 (3.3, 10.8)	0.83 (0.69, 0.91)	0.37 (0.05, 0.58)
2005	33.8 (26.0, 41.6)	109.1 (62.4, 155.9)	21.5 (14.3, 28.6)	5.1 (3.0, 8.7)	0.80 (0.66, 0.89)	0.36 (0.22, 0.48)
2006	30.9 (23.4, 38.3)	97.9 (55.9, 139.9)	19.4 (12.6, 26.2)	5.0 (2.9, 8.8)	0.80 (0.65, 0.89)	0.37 (0.12, 0.55)
2007	31.1 (23.7, 38.5)	67.0 (40.2, 93.9)	21.5 (14.4, 28.5)	3.1 (1.9, 5.2)	0.68 (0.46, 0.81)	0.31 (0.15, 0.44)
2008	25.9 (19.2, 32.5)	56.2 (31.1, 81.4)	17.2 (11.0, 23.4)	3.3 (1.8, 5.8)	0.69 (0.46, 0.83)	0.33 (0.02, 0.55)
2009	35.1 (27.4, 42.8)	72.8 (36.6, 109.0)	29.5 (21.5, 37.5)	2.5 (1.4, 4.4)	0.60 (0.29, 0.77)	0.16 (0.00, 0.30)
2010	29.1 (22.2, 36.0)	81.0 (43.8, 118.3)	19.2 (12.8, 25.5)	4.2 (2.4, 7.5)	0.76 (0.58, 0.87)	0.34 (0.07, 0.53)
2011	31.9 (24.6, 39.2)	100.6 (59.7, 141.5)	17.6 (11.4, 23.7)	5.7 (3.3, 9.8)	0.83 (0.70, 0.90)	0.45 (0.24, 0.60)
2012	37.7 (29.7, 45.6)	129.2 (76.3, 182.0)	22.6 (15.7, 29.6)	5.7 (3.4, 9.5)	0.82 (0.71, 0.89)	0.40 (0.25, 0.52)
2013	33.4 (25.9, 40.9)	119.0 (65.8, 172.3)	22.2 (15.3, 29.1)	5.4 (3.1, 9.3)	0.81 (0.68, 0.89)	0.34 (0.14, 0.49)
2014	31.4 (24.2, 38.6)	74.4 (39.3, 109.6)	22.9 (16.0, 29.9)	3.2 (1.9, 5.7)	0.69 (0.46, 0.82)	0.27 (0.04, 0.45)
2015	37.0 (29.3, 44.7)	118.1 (67.2, 169.1)	26.5 (19.1, 34.0)	4.5 (2.7, 7.4)	0.78 (0.62, 0.87)	0.28 (0.12, 0.41)
2016	39.0 (31.1, 46.9)	140.5 (80.6, 200.4)	24.6 (17.5, 31.7)	5.7 (3.4, 9.6)	0.82 (0.71, 0.90)	0.37 (0.23, 0.49)
Men						
2002	37.8 (24.7, 50.9)	131.0 (57.9, 204.1)	22.4 (11.7, 33.2)	5.8 (2.8, 12.2)	0.83 (0.64, 0.92)	0.41 (0.28, 0.51)
2003	56.6 (39.2, 74.0)	134.4 (67.1, 201.8)	44.1 (25.1, 63.1)	3.0 (1.6, 5.9)	0.67 (0.36, 0.83)	0.22 (0.08, 0.34)
2004	35.2 (22.9, 47.5)	130.0 (56.5, 203.5)	20.9 (10.4, 31.4)	6.2 (2.9, 13.3)	0.84 (0.66, 0.92)	0.41 (0.00, 0.70)
2005	46.8 (32.0, 61.5)	133.7 (65.0, 202.5)	31.2 (16.9, 45.5)	4.3 (2.2, 8.5)	0.77 (0.54, 0.88)	0.33 (0.15, 0.48)
2006	38.4 (25.2, 51.6)	122.5 (55.3, 189.7)	23.7 (11.1, 36.3)	5.2 (2.4, 11.1)	0.81 (0.58, 0.91)	0.38 (0.00, 0.65)
2007	40.5 (27.3, 53.8)	83.5 (36.3, 130.6)	31.6 (17.7, 45.5)	2.6 (1.3, 5.4)	0.62 (0.22, 0.81)	0.22 (0.04, 0.37)
2008	41.8 (28.4, 55.3)	94.1 (44.8, 143.3)	28.3 (15.2, 41.4)	3.3 (1.7, 6.7)	0.70 (0.39, 0.85)	0.32 (0.00, 0.54)
2009	50.3 (36.1, 64.5)	100.4 (33.3, 167.5)	45.6 (29.9, 61.2)	2.2 (1.0, 4.7)	0.55 (0.04, 0.79)	0.09 (0.00, 0.32)
2010	41.2 (28.4, 54.1)	123.0 (52.3, 193.7)	27.5 (15.3, 39.7)	4.5 (2.2, 9.3)	0.78 (0.54, 0.89)	0.33 (0.00, 0.55)
2011	43.4 (30.5, 56.3)	130.3 (65.2, 195.4)	23.8 (12.7, 35.0)	5.5 (2.8, 10.8)	0.82 (0.64, 0.91)	0.45 (0.15, 0.65)
2012	53.2 (38.8, 67.7)	183.9 (91.2, 276.5)	33.1 (20.0, 46.3)	5.5 (2.9, 10.5)	0.82 (0.66, 0.91)	0.38 (0.20, 0.51)
2013	46.3 (33.1, 59.4)	146.8 (63.0, 230.6)	32.7 (20.1, 45.4)	4.5 (2.2, 8.9)	0.78 (0.56, 0.89)	0.29 (0.01, 0.49)
2014	46.2 (33.1, 59.4)	79.6 (31.2, 127.9)	38.1 (24.1, 52.1)	2.1 (1.0, 4.2)	0.52 (0.03, 0.76)	0.18 (0.00, 0.38)
2015	63.7 (48.3, 79.1)	143.8 (67.2, 220.4)	52.3 (35.8, 68.8)	2.7 (1.5, 5.1)	0.64 (0.32, 0.80)	0.18 (0.14, 0.22)
2016	56.3 (41.9, 70.6)	206.2 (102.5, 309.9)	34.3 (21.3, 47.4)	6.0 (3.2, 11.3)	0.83 (0.69, 0.91)	0.39 (0.22, 0.52)
Women						
2002	20.1 (12.0, 28.2)	60.5 (11.3, 109.6)	12.2 (5.2, 19.2)	5.0 (1.8, 13.4)	0.8 (0.46, 0.93)	0.39 (0.19, 0.55)
2003	24.2 (15.1, 33.2)	89.1 (22.7, 155.6)	15.3 (7.1, 23.4)	5.8 (2.3, 14.6)	0.83 (0.57, 0.93)	0.37 (0.00, 0.61)
2004	20.8 (12.7, 28.9)	79.1 (14.1, 144.0)	13.9 (6.5, 21.3)	5.7 (2.1, 15.1)	0.82 (0.53, 0.93)	0.33 (0.00, 0.66)
2005	24.9 (16.0, 33.9)	89.9 (24.3, 155.4)	15.4 (7.5, 23.3)	5.8 (2.4, 14.2)	0.83 (0.58, 0.93)	0.38 (0.15, 0.55)
2006	25.6 (16.7, 34.6)	74.8 (23.6, 125.9)	17.6 (9.2, 26.0)	4.3 (1.8, 9.8)	0.77 (0.46, 0.90)	0.31 (0.04, 0.51)
2007	23.6 (15.1, 32.1)	48.7 (23.3, 74.1)	14.5 (7.2, 21.9)	3.4 (1.6, 6.9)	0.70 (0.38, 0.86)	0.38 (0.15, 0.55)
2008	15.7 (8.6, 22.8)	26.6 (7.6, 45.6)	10.9 (4.5, 17.4)	2.4 (1.0, 6.2)	0.59 (0.00, 0.84)	0.30 (0.00, 0.59)
2009	23.5 (15.2, 31.9)	46.8 (19.9, 73.7)	17.4 (9.3, 25.5)	2.7 (1.3, 5.6)	0.63 (0.22, 0.82)	0.26 (0.12, 0.38)
2010	21.6 (13.7, 29.5)	45.7 (20.1, 71.3)	14.2 (7.0, 21.4)	3.2 (1.5, 6.9)	0.69 (0.34, 0.85)	0.34 (0.00, 0.61)

Table 2 (continued)

Variable	IRs ^a (95% CI) per 100,000 PY			Relative and attributable risks (95% CI)		
	IRt	IRd	IRn	RR	ARE	PAR
2011	21.9 (14.0, 29.8)	73.5 (23.4, 123.7)	11.9 (5.4, 18.4)	6.2 (2.6, 14.8)	0.84 (0.61, 0.93)	0.45 (0.01, 0.70)
2012	24.8 (16.4, 33.3)	76.1 (25.8, 126.3)	14.7 (7.5, 21.9)	5.2 (2.3, 11.8)	0.81 (0.56, 0.92)	0.41 (0.07, 0.62)
2013	22.0 (13.9, 30.1)	91.8 (26.4, 157.2)	13.1 (6.2, 19.9)	7.0 (2.9, 17.1)	0.86 (0.66, 0.94)	0.41 (0.00, 0.66)
2014	20.5 (12.6, 28.3)	71.1 (20.0, 122.3)	12.2 (5.5, 18.9)	5.8 (2.4, 14.4)	0.83 (0.58, 0.93)	0.40 (0.00, 0.68)
2015	18.2 (10.8, 25.5)	98.3 (30.7, 165.8)	9.0 (3.4, 14.7)	10.9 (4.3, 27.6)	0.91 (0.77, 0.96)	0.50 (0.00, 0.78)
2016	26.0 (17.4, 34.6)	79.8 (20.3, 139.4)	17.9 (9.9, 25.8)	4.5 (1.9, 10.6)	0.78 (0.47, 0.91)	0.31 (0.01, 0.52)

^a Standardised to the German population, 2009

IRt, all cases of RRT in total population; IRd, cases of RRT in individuals with diabetes in population with diabetes; IRn, cases of RRT in individuals without diabetes in population without diabetes; RR relative risk (IRd/IRn); ARE, attributable risk of RRT due to diabetes among the population with diabetes ($[(IRd - IRn)/IRd]$); PAR, attributable risk of RRT due to diabetes in total population ($[(IRt - IRn)/IRt]$)

East German diabetes registry, the data of which are from the late 1980s when prevalence was quite low [23]. In contrast, diabetes prevalence was estimated in the current study using more recent data from nationwide German surveys with a substantially higher diabetes prevalence, partly due to the inclusion of undetected diabetes cases [14, 17]. However, the IRs among people without diabetes were comparable between the two studies (21.8 [95% CI 20.0, 23.6] in the present study vs 20 [95% CI 18, 23] in the previous study). Therefore, when comparing the incidence of RRT among people with and without diabetes, relative risk was considerably lower in the current study (almost fourfold) than in the previous study (almost eightfold).

An international comparison revealed one population-based study from Canada conducted in 1999–2000 with a comparable study design. The age- and sex-adjusted IR in the population with diabetes in that study was 132.9 per 100,000 PY and thus in line with our findings. In contrast, the IR among people without diabetes in the Canadian study was 11.0 and therefore much lower than our results, with a resulting higher corresponding RR of 12 [3].

Although some other studies also analysed the IR of RRT among people with diabetes and took into account diabetes as a comorbidity, they represented only the crude IRs [10, 11] or crude RRs [2], and were therefore not wholly comparable with our results.

Due to the fact that renal registers usually record only the primary cause for RRT, the epidemiological studies based on these data sources are only able to estimate the incidence of RRT that was due to diabetic nephropathy [5, 24–28]. Moreover, most of these studies reported IRs of diabetic nephropathy by using the total population as a denominator and not the population with diabetes at risk [5, 24, 26, 28]. This approach has limitations since it does not consider the prevalence of diabetes in the background population. These studies are therefore not comparable with the current study. Only one study from the USA [25] reported age-standardised IRs of diabetic nephropathy including estimation of the population with diabetes at risk: the IR varied between 260.2 per 100,000 PY in 2000 and 173.9 in 2014 [25]. A study from Catalonia, Spain, reported that the crude IR changed from 48.95 per 100,000 PY in 1994 to 59.36 in 2010 [27].

Fig. 1 Time trend of age- and sex-standardised IRs of first RRT (including 95% CI) in men and women with and without diabetes

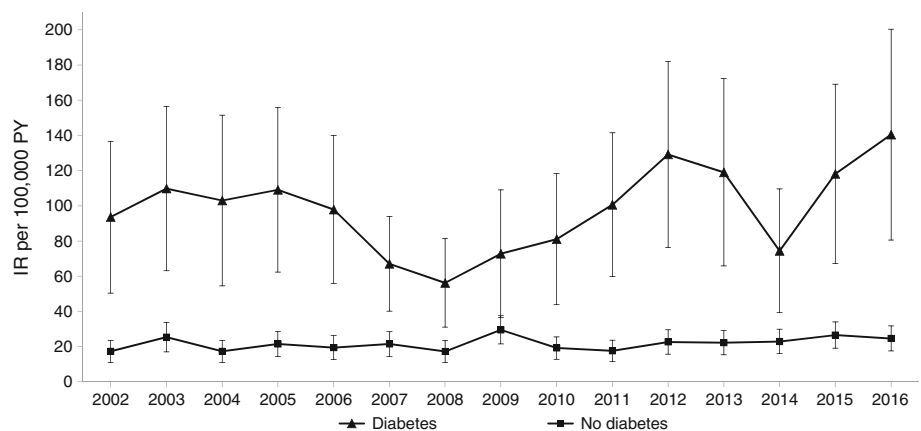


Table 3 Results of Poisson models: RRs for RRT, district of Mettmann, 2002–2016

Variable	RR for RRT (95% CI)		
	Both sexes	Men	Women
Model 1a (population with diabetes)			
Calendar year	1.02 (0.99, 1.04)	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)
Men vs women	2.29 (1.89, 2.78) *	–	–
Age (years) ^a			
≥ 80	19.88 (14.90, 26.53) *	2.70 (1.93, 3.78) *	3.89 (2.43, 6.23) *
70–79	12.00 (9.10, 15.81) *	2.46 (1.84, 3.28) *	3.55 (2.25, 5.61) *
60–69	4.63 (3.39, 6.32) *	1.77 (1.31, 2.41) *	2.52 (1.53, 4.15) *
Model 1b (population without diabetes)			
Calendar year	1.01 (0.99, 1.03)	1.03 (0.999, 1.06)	0.99 (0.96, 1.03)
Men vs women	1.67 (1.43, 1.94) *	–	–
Age (years) ^a			
≥ 80	3.04 (2.33, 3.96) *	25.52 (17.13, 38.02) *	13.41 (9.05, 19.86) *
70–79	2.76 (2.16, 3.51) *	15.25 (10.52, 22.12) *	7.86 (5.26, 11.74) *
60–69	1.97 (1.52, 2.55) *	5.33 (3.50, 8.13) *	3.67 (2.36, 5.70) *
Model 2 (entire population)			
Calendar year	1.01 (0.995, 1.03)	1.02 (0.99, 1.04)	1.00 (0.98, 1.03)
Diabetes (yes vs no)	3.57 (3.09, 4.13) *	3.25 (2.64, 4.01) *	4.14 (3.39, 5.06) *
Men vs women	1.98 (1.72, 2.29) *	–	–
Age (years) ^a			
≥ 80	10.40 (8.19, 13.22) *	11.55 (8.13, 16.41) *	8.80 (6.36, 12.16) *
70–79	7.60 (6.07, 9.52) *	8.30 (6.03, 11.41) *	6.52 (4.74, 8.97) *
60–69	4.00 (3.14, 5.09) *	4.24 (3.01, 5.96) *	3.67 (2.60, 5.19) *
Model 3 (entire population – including interaction term)			
Calendar year	1.02 (0.997, 1.04)	1.03 (1.002, 1.07)	1.00 (0.97, 1.03)
Diabetes (yes vs no)	3.95 (3.04, 5.14) *	4.30 (2.84, 6.51) *	3.72 (2.55, 5.43) *
Men vs women	2.00 (1.72, 2.27) *	–	–
Age (years) ^a			
≥ 80	10.4 (8.20, 13.25) *	11.57 (8.19, 16.46) *	8.81 (6.40, 12.28) *
70–79	7.60 (6.09, 9.55) *	8.30 (6.08, 11.47) *	6.53 (4.77, 9.06) *
60–69	3.99 (3.14, 5.09) *	4.21 (3.01, 5.94) *	3.68 (2.61, 5.23) *
Diabetes × calendar year	0.98 (0.95, 1.02)	0.96 (0.92, 1.01)	1.01 (0.97, 1.06)

^a Baseline: <60 years**p* < 0.05

The incidence of RRT considering only diabetic nephropathy in the current study was largely comparable to the study results from Catalonia, Spain [27], but approximately five times lower than the study from the USA [25].

We did not find any significant time trend regarding IRs or RRs during the study period 2002–2016.

Our results are in line with a study from Italy, which analysed the incidence of dialysis during the years 2004–2013 in the populations with and without diabetes and did not observe a significant change [2]. In contrast, a study from Hong Kong reported a significant decrease in the incidence of ESRD (4% per year in the fully adjusted model) among individuals with type 2 diabetes during the years 2000–2012 [11].

The studies that only counted diabetic nephropathy as a reason for RRT reported a decrease of RRT incidence. A study from the USA reported a reduction of about a third between 2000 and 2014 [25] and the study from Catalonia, Spain, reported a slight decrease since 2002 [27]. In our study we observed a significant decrease among men but not among women with diabetes (ESM Table 4).

Strengths and weaknesses of the study Several limitations have to be considered. First, we analysed the data from one regional dialysis centre in Germany that covered a population of about 310,000 inhabitants. Therefore, only a restricted generalisation of the data to the whole German population

was possible. However, the results of RRT incidence with respect to the whole population of the study region in 2006 were justifiably comparable to national German data: 254 per million population vs 213 per million population [20]. Second, the diabetic population as a population at risk was estimated using data from two nationwide German surveys performed in 1997–1999 and 2008–2011. Although regional differences are reported in diabetes prevalence in Germany, a recent analysis based on nationwide claims data revealed that the prevalence of diabetes in the study region was highly comparable to national diabetes prevalence [29]. Third, diabetes prevalence could only be estimated up until 2011, and thus for the main analysis we assumed that diabetes prevalence increased linearly as of 2011. Nevertheless, we also performed a sensitivity analysis using constant diabetes prevalence for the years 2011–2016 with no effect on the main results. Finally, we cannot rule out that some people from the study region started RRT outside of the study region, which would lead to an underestimation. However, individuals with ESRD receive dialysis at least once a week over a long time period. Most therefore prefer to travel only a short distance within the study region. We therefore assume that the collection of RRT cases in the study region is largely complete.

A main strength of our study was that we estimated the incidence of RRT in people with diabetes compared with people without diabetes independently of the underlying reason for RRT. The majority of studies published were able to identify only people with diabetes in whom diabetic nephropathy was the main reason for RRT. This methodological approach could lead to an underestimation of people with diabetes, since diabetic nephropathy was only reported as primary renal disease in approximately half of the individuals with type 2 diabetes [30]. An additional problem is that although diagnosis of diabetic nephropathy is based on established guidelines [22], in practice it is not always easy (especially among individuals with type 2 diabetes) to differentiate between diabetic nephropathy as a main reason for ESRD and diabetes as a comorbidity when other diseases in individuals with diabetes co-exist, e.g. hypertension or renal disease with nondiabetic pathogenesis [30, 31]. A biopsy could clarify the diagnosis of diabetic nephropathy but is usually only performed among a small group of individuals [30, 31]. All of these factors could lead to an over- or underestimation of diabetic nephropathy as a reason for ESRD. A further strength of our study was the population-based design. We conducted our study using valid data from one well-documented regional dialysis centre. We were therefore able to report clinical data relating to diabetes type and diabetes duration as well as comorbidities upon commencement of RRT. Finally, we estimated the IR over a long study period which allowed us to evaluate a time trend of 15 years.

Unanswered questions and future research The IR of RRT remained substantially higher among people with diabetes, with an almost fourfold-increased RR. Men have a twofold-increased risk of RRT compared with women. The IRs among the subpopulations with and without diabetes and the RRs during the study period largely remained mainly constant, with consistent results in both sexes. However, the considered study region was fairly small. Therefore, future research in a nationwide population is needed to confirm these findings.

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Data availability The data that support the findings of this study are available from the authors upon reasonable request and with permission of the dialysis centre of Mettmann.

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