

# Incidence of End-stage Renal Disease in Patients With Type 1 Diabetes

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**D**IABETIC NEPHROPATHY IS one of the most devastating complications in patients with type 1 diabetes, being the major predictor of premature death.<sup>1,2</sup> One third of patients develop microalbuminuria and about 15% to 25% develop persistent proteinuria during the first 20 years of living with the disease.<sup>1,3-5</sup> Notably, the cumulative incidence of hospitalization due to diabetic nephropathy has been reported to be 20% at 24 years after diagnosis of type 1 diabetes.<sup>6</sup> In general, the incidence of diabetic nephropathy seems to be lower in patients whose diagnosis occurred in more recent years.<sup>1,4,7</sup>

Although its incidence has decreased, diabetes is still the most important cause of end-stage renal disease (ESRD) in industrialized countries.<sup>8</sup> In Finland, type 1 diabetes accounts for two thirds of diabetic ESRD cases.<sup>9</sup> The cumulative incidence of ESRD has varied from 4% to 17% at 20 years after diagnosis, and after 30 years it has been shown to be 16%.<sup>3,10,11</sup> It is of note that earlier studies on risk of ESRD have been rather small and based on patients from single centers<sup>3,11</sup> or on prevalence cohorts instead of incidence cohorts.<sup>10</sup> Thus, large population-based studies with long-term follow-up have not yet been performed; therefore, the true incidence and age- and sex-stratified risk estimates of ESRD

**Context** End-stage renal disease (ESRD) is one of the most severe complications of type 1 diabetes. Yet, data on patients' risk of developing ESRD are sparse.

**Objectives** To estimate the long-term risk of developing ESRD and to assess how age at diagnosis of diabetes, time period of diagnosis, and sex affect the risk.

**Design, Setting, and Patients** A cohort of all patients younger than 30 years diagnosed as having type 1 diabetes in Finland in 1965-1999 (n=20 005) was identified from the Finnish Diabetes Register. The cohort was followed up from diagnosis of diabetes until development of ESRD (dialysis or kidney transplantation as identified from the Finnish Registry for Kidney Diseases), death, or end of follow-up on December 31, 2001.

**Main Outcome Measure** Cumulative incidence of ESRD, accounting for death as a competing risk.

**Results** The cohort was followed up for maximally 37 years, with a median of 16.7 years. During 346 851 person-years, 632 patients developed ESRD. The cumulative incidence of ESRD was 2.2% at 20 years and 7.8% at 30 years after diagnosis. The risk of developing ESRD was lowest in patients whose diagnosis occurred at younger than 5 years. The risk of ESRD was lower for patients diagnosed as having type 1 diabetes in later years. The risk did not differ significantly between sexes.

**Conclusions** With regard to ESRD, the prognosis of type 1 diabetes has improved during the past 4 decades. Children diagnosed as having diabetes before age 5 years have the most favorable prognosis. Overall, incidence of ESRD appears to be lower than previously estimated.

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among patients with type 1 diabetes are not known.

In type 1 diabetes, proteinuria is associated with cardiovascular complications that account for the majority of early mortality,<sup>12</sup> but in earlier years, the main cause of death among these patients was uremia.<sup>1,2</sup> However, the cumulative survival of patients diagnosed as having type 1 diabetes before 18 years of age has improved over time and was reported to be 95% to 97% at 20 years after diagnosis.<sup>13</sup> Our objectives for the current study were to estimate the long-term risk of ESRD and death in patients with type 1 diabetes and to study how age at diagnosis of diabetes, time period of diagnosis, and sex affect these risks. We were able to do

so by combining information from 3 Finnish nationwide population-based registries.

## METHODS

### Study Population

Patients with type 1 diabetes were identified within the Finnish Diabetes Register, which covers almost 100% of all patients with this type of diabetes in

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Finland.<sup>14</sup> The cohort comprised all patients diagnosed as having type 1 diabetes in 1965-1999 before age 30 years. The register is based on the Central Drug Registry's records of approvals of free-of-charge medications. In Finland, insulin treatment for diabetes has been free since 1964. To qualify as a type 1 diabetes diagnosis, insulin treatment had to have been started at the time of diagnosis and continued for at least 1 year and patients had to have been younger than 30 years at the time of diagnosis. These criteria have remained unchanged over the course of the study. Information on ESRD through 2001 was obtained from the Finnish Registry for Kidney Diseases.<sup>9</sup> This registry has an estimated 97% to 99% coverage of all patients accepted for renal replacement therapy (dialysis or kidney transplantation) in Finland since 1965. Information on deaths through 2000 was acquired by database linkage with the Population Register Centre in Finland. The database linkage was possible because of the Finnish system of unique personal identification numbers for all citizens.

The study is purely based on information derived from national registries. The Finnish Diabetes Register is maintained by the National Public Health Institute, a governmental institution. The Finnish Registry for Kidney Diseases is maintained by the Finnish Association for Organ-Transplant and Kidney Patients and is also fully financed by the Finnish government. All data were obtained with written informed consent from the patients, including the understanding that such data were to be analyzed and included anonymously in registry reports and scientific publications.

### Statistical Methods

Patients were followed up from diagnosis of type 1 diabetes until occurrence of ESRD (dialysis or kidney transplantation), death, or end of follow-up on December 31, 2001. Cumulative incidence of ESRD was calculated with a method that takes into account the effect of death as a competing risk event, as de-

scribed by Kalbfleisch and Prentice.<sup>15</sup> The method allows for the fact that patients who die are no longer at risk of ESRD. This differs from the cumulative incidence estimated by the Kaplan-Meier method, which in this case would introduce bias because it would erroneously assume that those who die remain at risk in the future. Patients were censored on December 31, 2001. Incidence of all-cause mortality was estimated using Kaplan-Meier survival probabilities (1 - survival probability). In the analysis of mortality, death due to any cause was the event and patients were censored on December 31, 2001.

The incidence rate of ESRD was calculated as number of ESRD cases divided by number of patient-years (in thousands) during 5-year periods of follow-up. Adjusted relative risks of ESRD associated with sex, age at diagnosis, and time period of diagnosis were estimated by fitting a proportional subdistribution hazards regression model that takes death into account as a competing risk event.<sup>16</sup> Adjusted relative risks of death were calculated using Cox regression analysis. All possible interactions between the explanatory variables were tested and found to be statistically nonsignificant. The effect of ESRD on risk of death was studied by including ESRD as a time-dependent variable in Cox regression.

The R statistical software, version 1.7.0 (The R Foundation for Statistical Computing, Vienna, Austria; available at <http://www.r-project.org>) with the "cmprsk" package was used for analysis of cumulative incidence ("cuminc" function) and for proportional subdistribution hazards regression ("crr" function). An extended Cox regression model with a time-dependent variable (ESRD) was constructed using Stata statistical software, release 8.0 (Stata Corp, College Station, Tex). All other analyses were performed using SPSS 12.0.1 for Windows (SPSS Inc, Chicago, Ill).

### RESULTS

In 1965-1999, 20 005 patients in Finland younger than 30 years were diag-

nosed as having type 1 diabetes (TABLE 1). The median follow-up time after diagnosis was 16.7 (range, 0-37.0) years. During 346 851 person-years of follow-up, 632 cases of ESRD and 1417 deaths were identified (TABLE 2).

FIGURE 1 depicts the cumulative incidence of ESRD according to sex and age at diagnosis of type 1 diabetes. The cumulative incidence among all type 1 diabetic patients was 2.2% (95% confidence interval [CI], 1.9%-2.5%) after 20 years and 7.8% (95% CI, 7.1%-8.5%) after 30 years of follow-up. Correspondingly, the cumulative incidence was 2.1% (1.7%-2.5%) and 8.3% (7.3%-9.3%) for males and 2.2% (1.7%-2.6%) and 7.8% (6.7%-8.8%) for females. Patients of both sexes diagnosed as having type 1 diabetes before age 5 years had a smaller risk of developing ESRD (3.3% after 30 years; 95% CI, 1.7%-4.9%) than did other patients (8.4%; 95% CI, 7.6%-9.2%).

FIGURE 2 shows the crude incidence rate of ESRD. Within 15 years of diagnosis of diabetes, ESRD was rare. Thereafter, the incidence rate increased rapidly. After 20 years of follow-up, the incidence rate reached a plateau, which was higher for those diagnosed as having diabetes during an earlier time period. Between 20 and 30 years after the diagnosis of type 1 diabetes, the average incidence rate was 7.3 ESRD cases (95% CI, 6.4-8.3) per 1000 patient-years for males and 5.5 cases (95% CI, 4.6-6.5) per 1000 patient-years for females (rate difference, 1.8; 95% CI, 0.5-3.2).

In multivariate analysis, age at onset and time period of diagnosis affected the risk of developing ESRD, whereas sex did not (TABLE 3). Patients aged 0 to 4 years had a lower risk than patients in other age groups. Patients diagnosed as having type 1 diabetes between 1965 and 1969 had the highest risk of ESRD; thereafter, the prognosis has continuously improved.

The cumulative mortality was 6.8% (95% CI, 6.3%-7.2%) at 20 years and 15.0% (14.1%-15.9%) at 30 years after diagnosis of type 1 diabetes (FIGURE 3). The most deaths (in absolute numbers)

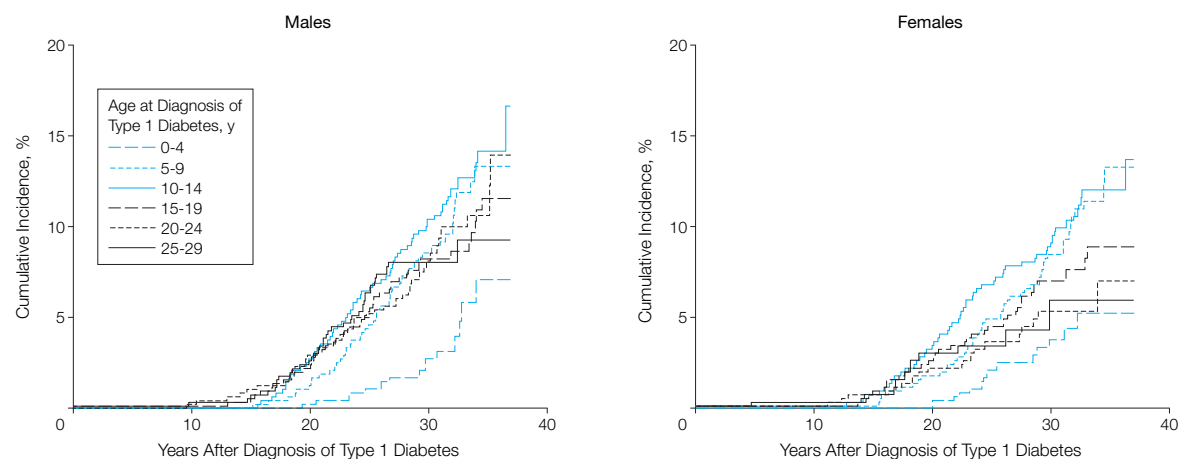
**Table 1.** Number of Males and Females Diagnosed as Having Type 1 Diabetes in Finland According to Age and Time Period of Diagnosis

Age at Diagnosis of Type 1 Diabetes, y, by Sex	Time Period of Diagnosis of Type 1 Diabetes						Total
	1965-1969	1970-1974	1975-1979	1980-1984	1985-1989	1990-1994	
0-4							
M	140	153	152	203	213	261	1434
F	145	115	135	157	176	256	1283
5-9							
M	245	267	277	313	348	353	2217
F	234	249	261	280	281	339	2090
10-14							
M	373	368	384	380	368	367	2740
F	313	315	305	300	263	310	2176
15-19							
M	287	287	284	248	225	245	1841
F	179	204	137	156	141	139	1099
20-24							
M	220	232	213	225	237	219	1566
F	138	132	114	150	150	155	962
25-29							
M	103	200	244	275	332	300	1765
F	46	77	89	125	149	174	832
Total	2423	2599	2595	2812	2883	3118	20 005

**Table 2.** Number of Patients With Type 1 Diabetes, Person-Years of Follow-Up, ESRD Cases, and Deaths According to Sex and Age Group

Age Group, y	Males				Females			
	No. of Patients	Person-Years of Follow-up*	No. With ESRD	No. of Deaths	No. of Patients	Person-Years of Follow-up*	No. With ESRD	No. of Deaths
0-4	1434	23 426	14	29	1283	20 665	14	29
5-9	2217	37 995	68	101	2090	35 508	64	70
10-14	2740	48 890	119	198	2176	40 411	97	102
15-19	1841	34 525	72	185	1099	21 716	40	62
20-24	1566	27 475	59	220	962	17 349	22	87
25-29	1765	26 667	49	272	832	12 224	14	62
Total	11 563	198 978	381	1005	8442	147 873	251	412

\*Time from diagnosis of type 1 diabetes to end-stage renal disease (ESRD) onset, death, or end of follow-up.

**Figure 1.** Cumulative Incidence of End-stage Renal Disease Among Male and Female Patients With Type 1 Diabetes According to Age at Diagnosis of Diabetes

occurred among patients who had not developed ESRD. The cumulative risk of dying with ESRD was 0.7% (95% CI, 0.5%-0.8%) at 20 years and 3.3% (2.9%-3.8%) at 30 years after diagnosis of type 1 diabetes. However, it is noteworthy that patients with ESRD had a relative risk of 13.1 (95% CI, 11.1-15.3) compared with other patients with type 1 diabetes when adjusting for age, sex, and time period of diabetes diagnosis. Notably, male patients had a 66% higher risk of death due to any cause (Table 3). The risk of death increased with age at diagnosis. The time period for the diagnosis of diabetes strongly affected survival: patients with diagnosis in 1975-1979 had 48% lower risk of dying than those with diagnosis in 1965-1969.

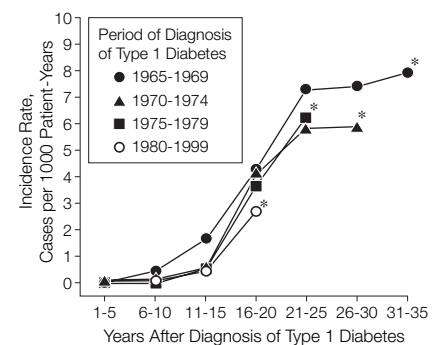
## COMMENT

We found that the cumulative incidence (risk) among patients with type 1 diabetes for development of ESRD within 30 years was approximately 7.8%, which is lower than previously reported.<sup>3,11</sup> In patients whose diagnosis of diabetes occurred before age 5 years, the risk was found to be considerably lower. The risk was also lower for patients whose diagnosis occurred in more recent years.

Our estimates are based on data linkage among 3 nationwide Finnish registry databases, all of which are almost 100% complete. Therefore, virtually all Finnish inhabitants diagnosed as having type 1 diabetes before age 30 years were followed up until start of dialysis, kidney transplantation, death, or end of follow-up in 2001. Our study includes more than 20 000 patients with type 1 diabetes, of whom 632 cases developed ESRD, and the study is, to date, the largest one estimating risk of ESRD in type 1 diabetes. Two earlier studies on incidence cohorts have been published, one including 292 patients with type 1 diabetes and 44 cases of ESRD<sup>3</sup> and the other comprising 142 patients, of whom 25 developed ESRD.<sup>11</sup> Another study estimated risk of ESRD in 2 populations with type 1 diabetes.<sup>10</sup> Altogether, 2369 patients were included and 109 ESRD cases were identified. However, the patients were not followed up from the time of diagnosis; therefore, the cumulative risk of ESRD after diagnosis of type 1 diabetes could not be estimated appropriately. Our study is the first population-based study in which cumulative risk of ESRD in patients with type 1 diabetes has been estimated. The large number of patients in our study enables

group comparisons that have not been feasible in earlier studies. Our study shows for the first time a reduced risk of ESRD in patients diagnosed as having type 1 diabetes before age 5 years. The finding that risk of ESRD has decreased over time is also new. Notably, our study population represents a country with a fairly homogeneous health care system. Furthermore, virtually all patients are white. Thus, the data may not be reflective of other eth-

**Figure 2.** Incidence Rate of End-stage Renal Disease According to Time Period of Diagnosis of Type 1 Diabetes



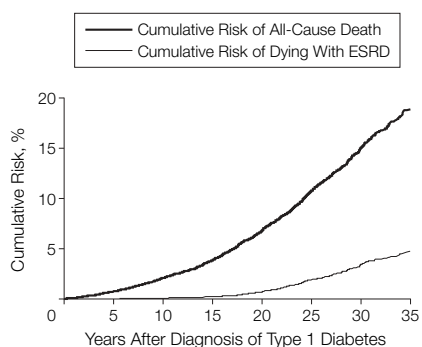
The incidence rate was calculated as number of end-stage renal disease cases per 1000 patient-years during 5-year follow-up periods after diagnosis of type 1 diabetes. The last data point of each curve (asterisks) represents a 7-year period (eg, 30-37 years for those diagnosed in 1965-1969).

**Table 3.** Relative Risks of ESRD and Death Associated With Sex, Age, and Time Period of Diagnosis of Type 1 Diabetes

Variables	No. With Type 1 Diabetes	Person-Years of Follow-up	ESRD		Death	
			Relative Risk (95% CI)*	P Value (df)	Relative Risk (95% CI)*	P Value (df)
Sex						
Female	8442	147 873	1.00	.13	1.00	.001
Male	11 563	198 978	1.13 (0.96-1.33)		1.66 (1.48-1.86)	
Age at onset, y						
0-4	2717	44 091	1.00	<.001 (5)	1.00	<.001 (5)
5-9	4307	73 503	2.73 (1.82-4.09)		1.75 (1.30-2.35)	
10-14	4916	89 301	3.34 (2.26-4.94)		2.34 (1.77-3.10)	
15-19	2940	56 241	2.55 (1.69-3.85)		2.88 (2.16-3.83)	
20-24	2528	44 824	2.49 (1.63-3.81)		4.87 (3.68-6.45)	
25-29	2597	38 891	2.83 (1.82-4.41)		7.42 (5.60-9.82)	
Time period of diagnosis of type 1 diabetes, y						
1965-1969	2423	74 487	1.00	<.001 (3)	1.00	<.001 (3)
1970-1974	2599	71 850	0.78 (0.64-0.94)		0.63 (0.55-0.72)	
1975-1979	2595	60 869	0.72 (0.57-0.90)		0.52 (0.44-0.61)	
1980-1999	12 388	139 644	0.47 (0.34-0.65)		0.41 (0.35-0.48)	

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease.

\*The relative risks were adjusted mutually for the other explanatory variables using proportional subdistribution hazards regression (ESRD) or Cox regression (death).

**Figure 3.** Cumulative Risk of Death After Diagnosis of Type 1 Diabetes

The difference between the curves is the cumulative risk of dying without end-stage renal disease (ESRD).

nic or racial groups or populations with different access to care and health care systems.

The risk of ESRD in Finland was lower than observed in previous studies. In a cohort from Allegheny County, Pennsylvania, the cumulative incidence of dialysis was reported to be 13% at 20 years after diagnosis of type 1 diabetes compared with 2.4% in our cohort.<sup>10</sup> The findings of Krolewski et al<sup>11</sup> were more similar to ours, with a 2% to 8% cumulative incidence of ESRD at 20 years and 15% to 17% at 30 years after diagnosis, depending on age at diagnosis. The incidence of type 1 diabetes in Finland is one of the highest in the world.<sup>17</sup> Because of this, much emphasis has been put on the Finnish diabetes care system, which has been nationally organized since the 1960s. It has been speculated that this may be the reason for the relatively good prognosis of Finnish patients with type 1 diabetes.<sup>18</sup> We further demonstrate that the prognosis with regard to ESRD has improved during the past decades. This is in line with earlier findings on persistent proteinuria,<sup>1,4,7</sup> but declining risk of ESRD has not previously been reported. This indicates that the development of diabetes care has been beneficial. Major milestones include the introduction of disposable syringes in the early 1970s, the development of home glucose monitoring and of semisynthetic and synthetic human insulin in the 1980s, and multiple insulin

injection regimens, the effect of which improved with the introduction of rapid-acting insulin in the 1990s.

The risk of persistent proteinuria and ESRD has been shown to be lower among patients diagnosed as having diabetes at younger than 10 years than among those whose diagnosis occurred during the ages of 10 and 20 years.<sup>3,4,11</sup> But, increased risk of ESRD among patients with diagnosis occurring at ages 5 to 9 years compared with those whose diagnosis occurred before age 5 years has not been reported previously. There are, however, some indications that patients diagnosed as having diabetes before age 5 years have lower rates of complications such as microalbuminuria, retinopathy, and hospitalization due to nephropathy.<sup>6,19,20</sup> The reasons are not known. One explanation may be that patients with early-onset diabetes are genetically different from those who develop diabetes later,<sup>21,22</sup> which also could lead to differences in the susceptibility to develop ESRD. There might be other explanations as well. Good self-management of diabetes correlates with good metabolic control.<sup>23</sup> Self-care is a skill that can be compared with other skills—such as speaking—and is better managed the earlier it is acquired. Children who become used to dealing with diabetes at an early age might adhere to the insulin treatment and diet better than those who face the requirements of diabetes at an older age.

We also analyzed the cumulative incidence of ESRD according to attained age. Patients whose diabetes was diagnosed at age 0 to 4 years reached the same risk of developing ESRD about 5 years later than those whose diagnosis occurred at age 5 to 9 years and 10 years later than those whose diagnosis occurred at age 10 to 14 years. Thus, patients diagnosed as having diabetes before age 15 years reached a similar risk of ESRD at virtually the same age (eg, 5% cumulative risk of ESRD at an approximate age of 33 years). This supports the notion that the prepubertal duration of diabetes contributes less than the postpubertal duration to the

risk of diabetic complications.<sup>20</sup> However, patients diagnosed as having diabetes at older than 15 years reached the same cumulative risk of ESRD at a considerably later stage in life.

Earlier studies have shown that only a subset of patients with diabetes (approximately one third) develop persistent proteinuria and that the incidence rate of this complication peaks between 15 and 20 years after diagnosis of type 1 diabetes, after which time it starts to decline.<sup>1-4</sup> One study also demonstrated decreasing incidence rates of ESRD after 20 years of diabetes duration.<sup>11</sup> In contrast, we found that the incidence rate of ESRD, after a rapid increase between 15 and 20 years after diagnosis of type 1 diabetes, reached a plateau and thereafter remained stable up to 35 years of follow-up. However, ESRD is an end point of nephropathy occurring on average 10 years later than proteinuria.<sup>3</sup> Decreases in the incidence rate of ESRD may become apparent only after even longer follow-up. The incidence rate of ESRD was virtually zero during the first 15 years after diagnosis of diabetes. Because more than 40% of the patients (n=8442) received diagnoses in 1987 or later and, thus, were followed up for less than 15 years, a substantial proportion of the patients did not contribute to the long-term risk estimates of ESRD. Notably, in these patients only 5 cases of ESRD occurred, showing that the risk of developing ESRD within 15 years of diabetes debut is almost nonexistent. This is probably a reflection of effective early prevention, which reduces the risk of developing nephropathy.<sup>5</sup>

For the calculation of cumulative incidence, we used methods that correct for death as a competing risk event. In contrast with the Kaplan-Meier method and the standard Cox regression, the methods used herein take into account that deceased patients no longer are at risk of developing ESRD. Thus, the statistical methods used herein consider that a high mortality rate reduces the risk of ESRD because the patients die before they develop the complication. When death was consid-



ered as a competing risk event, there was no statistically significant difference in risk of ESRD between male and female patients in multivariate analysis, whereas if the competing risk was not accounted for (Cox regression), males had 18% higher risk of ESRD than females. This is explained by the fact that male patients had considerably higher mortality and died more frequently before they developed ESRD. Thus, male patients could have had a greater risk of ESRD than female patients, if they had lived long enough to develop this complication.

Type 1 diabetes is associated with a considerable premature mortality.<sup>18</sup> The 20-year cumulative mortality of patients diagnosed as having diabetes before age 18 years was previously reported to be 3.1% in Finland, 4.6% in Israel, and 5.5% in a cohort in Allegheny County, Pennsylvania.<sup>13</sup> In this study, the same cumulative risk of death was 4.0%, which is comparable with the earlier findings. The risk of death was higher among males and patients with diagnosis occurring at an older age. Patients diagnosed as having diabetes in more recent years showed a considerably lower risk of dying. In earlier years, uremia was considered the most important cause of death among proteinuric diabetes patients.<sup>1,2</sup> In this study, approximately every fifth death during the first 30 years of follow-up occurred among patients who had developed ESRD. Among 222 deceased ESRD patients in this study, uremia was identified as the cause of death in only 1 patient, whereas cardiovascular complications caused two thirds of the deaths, which is in line with earlier findings on patients with diabetes who were successfully treated for renal failure.<sup>24</sup> However, because cardiovascular complications are known to be more common among patients with diabetes who have proteinuria,<sup>2,12</sup> nephropathy can serve as an indirect cause of mortality. This was evident in our study, which showed a 13-fold risk of death among patients with ESRD compared with other patients with type 1 diabetes. This emphasizes the severity of ESRD as a complication of diabetes.

In conclusion, our data indicate improved prognosis of type 1 diabetes with regard to both ESRD and death. Patients younger than 5 years at diabetes onset have the most favorable prognosis. The overall incidence of ESRD appears to be lower than previously reported.

**Author Contributions:** Dr Finne had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Finne, Reunanen, Grönhagen-Riska.

**Acquisition of data:** Finne, Reunanen, Stenman, Grönhagen-Riska.

**Analysis and interpretation of data:** Finne, Reunanen, Groop, Grönhagen-Riska.

**Drafting of the manuscript:** Finne, Reunanen, Stenman, Groop, Grönhagen-Riska.

**Critical revision of the manuscript for important intellectual content:** Finne, Reunanen, Groop, Grönhagen-Riska.

**Statistical analysis:** Finne, Reunanen, Grönhagen-Riska.

**Obtained funding:** Finne, Grönhagen-Riska.

**Administrative, technical, or material support:** Finne, Reunanen, Stenman, Grönhagen-Riska.

**Study supervision:** Finne, Reunanen, Grönhagen-Riska.

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