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Original article

End-stage renal disease: incidence and prediction by coronary heart disease, and educational level. Follow-up from diagnosis of childhood-onset type 1 diabetes throughout Norway 1973–2017

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ABSTRACT

Purpose: To investigate incidence of end-stage renal disease (ESRD), and the association of education and coronary heart disease (CHD) with ESRD, in subjects throughout Norway followed from the diagnosis of childhood-onset type 1 diabetes.
Methods: All new onset cases of type 1 diabetes 1973–2016 were followed for CHD and ESRD in nationwide registries through 2017. Ten matched controls per case were selected from the National Population Register. Cox regression was used to estimate hazard ratios, and probabilities were estimated by the cumulative incidence function accounting for competing risk.
Results: Among 9311 patients with type 1 diabetes, 130 developed ESRD with a probability of ESRD after 40 years of 5.5%. The rate was 35-fold higher than in controls (aHR = 35.5, 95% CI 23.1 – 54.6). Higher education was associated with lower risk of ESRD compared to low education (aHR = 0.14, 95% CI 0.07 – 0.27). Diagnosed CHD was associated with 14-fold increased rate of ESRD (aHR = 14.3, 95% CI 9.2 – 22.2).
Conclusions: The hazard rate of ESRD was 35-fold higher in cases compared to controls. CHD was associated with a 14-fold increased rate of subsequent ESRD, while higher education was associated with substantially lower rate of ESRD.

Introduction

Type 1 diabetes is one of the most common chronic diseases among children in Norway 0–14 years [1] and causes several complications including nephropathy and end-stage renal disease (ESRD)[2] in adult life. Although the incidence of diabetic nephropathy in type 1 diabetes is declining in many countries [3,4]. ESRD is a serious complication and imposes a high burden in terms of financial cost, quality of life and increased risk of comorbidity and mortality [5]. ESRD has been associated with increased risk of all-cause and cardiovascular mortality and cardiovascular disease (CVD) both in subjects with and without type 1 diabetes [6,7]. Orchard et. al reported the cumulative incidence of ESRD, diagnosed in the time-period 1965–1980, to be 14.5% after 30 years of duration of type 1 diabetes [8]. In the Diabetes Con-

Abbreviations: ESRD, End-stage renal disease; CKD, Chronic kidney disease; CHD, Coronary heart disease; CVD, Cardiovascular disease; SES, Socioeconomic status; RRT, Renal replacement therapy; BMI, Body mass index; CVDNOR, Cardiovascular disease of Norway; HbA1c, Glycated hemoglobin A1C; GFR, Glomerural filtration rate.

There are no potential conflicts of interest relevant to this article.

Disclosures: Data from the Norwegian Patient Registry and the Norwegian Cause of Death Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by these registries is intended, nor should be inferred.

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trol and Complications trial (DCCT) population after 17–18 years of follow-up (diabetes duration of 27–28 years), the cumulative incidence of ESRD was 2% and 1% in the conventional and intensive treatment groups, respectively [9]. It is established that people with diabetic kidney disease have increased risk of CHD, but there are fewer studies on how CHD influences the risk of ESRD in subjects with type 1 diabetes.

Socioeconomic status (SES) is inversely associated with many chronic diseases both in the general population, and in people with type 1 diabetes [10], where low SES also predicts diabetes complications [11]. There are many studies regarding SES and complications in type 1 diabetes, ranging from cross-sectional to prospective study designs and various definitions of SES. However, publications with updated trends in social inequality of the severe outcome ESRD in countries with universal health care systems are scarce.

Norway has a universal health care system and several nationwide health registers with virtually complete coverage. In a prospective cohort study of individuals with long-term follow-up from diagnosis of childhood-onset type 1 diabetes to the end of 2017, we had following aims:

1 To estimate the cumulative incidence of ESRD and compare it to matched controls.
2 To estimate the magnitude of association of both CHD and educational level with subsequent ESRD.

Material and methods

Participants and design

This is a secondary analysis of data from a prospective, nationwide cohort study of newly diagnosed childhood-onset type 1 diabetes, based on individual linkage of seven nation-wide registries with near complete coverage (Supplemental Figure S1). The cohort consists of 9311 patients with type 1 diabetes, diagnosed at age 0–14 years during 1973–2016, registered in the Norwegian Childhood Diabetes Registry with high completeness (91%)[12].

For each person with type 1 diabetes, up to 10 control subjects were randomly selected from the National Population Register matched for sex, age, county of residence and being alive at the time of type 1 diabetes onset in their counterpart. Initially selected controls who were later diagnosed with type 1 diabetes after age 15 years and registered in the Norwegian Patient Register (see below), were excluded from the analysis (n = 363). Six patients with ESRD in the control group without type 1 diabetes were registered in the Norwegian Renal Registry before enter date (diabetes onset of matching case) and also excluded from the analyses. While most type 1 diabetes cases got 10 matched controls, a few got only nine, leaving 91,153 controls for analysis.

Outcome

The primary outcome was ESRD, defined as renal failure requiring renal replacement treatment (RRT), at the first registration in the Norwegian Renal Registry (http://www.nephro.no).

There are 26 renal hospital units reporting annually to the Norwegian Renal Registry which includes all patients with established CKD requiring RRT including the modality (dialysis, type of dialysis, transplantation). RRT is offered at eGFR <10 ml/min/1.73m^2 and dialysis starts at eGFR 5–10 ml/min/1.73m^2. All patients in Norway who are eligible for RRT in Norway will be offered treatment free of cost. We have no knowledge of cases who did not accepted this offer. The data are annually crosschecked against the transplantation lists at Oslo University Hospital and with each of the 26 units. Oslo University Hospital, Rikshospitalet, is the only transplant center in Norway. The Norwegian Renal Registry reports more than 97% completeness of ascertainment (Annual Report 2017, Norwegian Renal Registry, Oslo University Hospital (https://www.kvalitetsregistre.no/registers/norsk-nyreregister). The diagnostic codes used in the registry are the same used as those used by the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry (www.era-edta.org/en). Any patient who develops ESRD are considered for potential kidney transplantation and referred to the transplant center. To undergo kidney transplantation in Norway, no discrimination is carried out with respect to the age of the patient. There are five inclusion criteria: 1) more than 2 years of life expectancy (in terms of general comorbidity and presumed chance of surviving surgery), 2) cardiac ejection fraction greater than 30%, 3) no known current malignancy (skin cancer and prostate cancer, apart from malignant melanoma is not part of this criterion), 4) if previous cancer: free from relapse for more than 1 year, 5) patients with BMI ≤30 kg/m^2 were accepted for kidney transplantation (in a few cases BMI up to 35 kg/m^2 was accepted for surgery based on individual assessments with high need of transplantation prior to weight reduction, for example, when dialysis treatment was considered difficult to implement).

At enrollment in the Norwegian Renal Registry, information about smoking and use of antihypertensive medication and statins are registered (Supplemental Table S1 & S2).

Codes and definitions of CHD are described in the next section.

Covariates

Information on CHD events for all participants was obtained by linkage to two nationwide registries consisting of hospitalization discharge diagnoses; the Cardiovascular Disease in Norway (CVDNOR) Project from time period 1994–2008 [13], and the Norwegian Patient Registry from 2008–2017 [14]. We defined the earliest date of registration of a CHD code as the date of CHD, including fatal events registered only in the Norwegian Cause of Death Registry. CHD was defined as The international Classification of Diseases 9th revision (ICD-9) codes 410 – 414 (myocardial infarction, acute and/or subacute and/or chronic forms of ischemic heart disease, angina pectoris) or ICD-10 codes I20 – I25 (angina pectoris, acute and/or subacute and/or chronic ischemic heart disease, myocardial infarction and complications to myocardial infarction)[15].

Statistics Norway provided information about educational level and country of origin for the participants. Country of origin is based on birth country of the subjects and their parents. If the individual and both parents were born in Norway, the country of origin is defined as Norway. If at least one of the parents or the individual were born outside of Norway, they are defined as non-Norwegian. Data on educational level achieved per 2016 (at end of follow-up), was categorized into lower (compulsory (≤10 years)), intermediate (11–13 years) and higher (≥14 years). There were missing data on education in 2307 subjects of whom 99.3% were born after year 2000 and thus had not yet completed their education (https://www.ssb.no/en). We evaluated whether education level, as an indicator of SES, modifies the future risk of ESRD among patients with type 1 diabetes.

Statistical analyses

In the primary analyses, individuals were followed from onset of type 1 diabetes until ESRD, emigration, death or end of 2017, whichever occurred first. To avoid immortal time bias, controls were also followed from the time of type 1 diabetes in the matched case. Analyses of associations between covariates and ESRD were done using Cox regression estimating hazard ratios with 95% confidence intervals. For the association between type

Table 1
Characteristics of patients followed from diagnosis of childhood-onset type 1 diabetes.

Characteristics	Total study cohort	ESRD	No-ESRD
Participants, N (%)*	9311 (100)	130 (100)	9181 (100)
Female sex, N (%)	4288 (46.1)	46 (35.4)	4242 (46.2)
Norwegian, N (%)†	8241 (88.5)	121 (93.1)	8119 (88.4)
Lower education, N (%)‡	2468 (26.5)	61 (46.9)	4714 (51.3)
Intermediate education, N(%)	2634 (28.3)	58 (44.6)	2576 (28.1)
Higher education	1902 (20.4)	11 (8.5)	1891 (20.6)
Age at end of follow-up, years (range)§	27.1 (1 – 59.5)	36.5 (17.7 – 52.3)	27.0 (0.8 – 59.5)
Age at onset of type 1 diabetes, years (range)¶	8.8 (0.1 – 15.0)	10.0 (0.4 – 14.9)	8.8 (0.1 – 15.0)
Duration of diabetes, years (range)‖	18.4 (0.03 – 45.0)	26.4 (12.1 – 44.0)	18.2 (0.03 – 45.0)
Died during follow-up, N (%)	327 (3.5)	35 (26.4)	288 (0.03)
Coronary heart event, N (%)	322 (3.5)	65 (48.9)	258 (0.03)

* The percentage (%) is computed by the total number of subjects with type 1 diabetes (=out of 9311) in row 1, by the total number of patients with ESRD in row 2 (=out of 130) and by the total number of subjects without ESRD in row 3 (=out of 9181).
† If the individual and both parents were born in Norway, the individual is defined as Norwegian,
‡ Lower education (Compulsory, ≤ 10 years), Intermediate (11–13 years), Higher level (≥14 years),
§ 1 subject followed for <1 year,
¶ 68 subjects diagnosed below <1 year of age,
‖ 8 subjects with duration <1 year.There were missing data on 2307 subjects of whom 99.3% were born after year 2000 and thus had not yet completed their education.

1 diabetes and ESRD, comparing patients with matched controls, we used stratified Cox regression where each set of a type 1 diabetes patient and matched controls formed a stratum. We estimated the probability of outcomes over time using the cumulative incidence function based on the Fine & Gray competing risk regression model, treating death as a competing risk [16]. CHD occurring before ESRD was modelled as a time-varying covariate, where individuals who developed CHD changed state at the first registered CHD event. When studying mortality, ESRD was modelled as time-varying covariate and death as event. In analysis of CHD after ESRD, ESRD was modelled as time-varying covariate and CHD as event.

Individuals could follow one of several paths from onset of type 1 diabetes via various complications (CHD, ESRD) to death, end of follow-up or emigration. We reported incidence proportions and estimated rates and probabilities of transitions between states as displayed in Figure 1. The covariates used in the Cox regression models were educational level (three levels), age (continuous) and calendar year at onset of type 1 diabetes (continuous), and sex. We used Stata version 15 for data analyses (StataCorp LP, College Station, TX).

Ethics statement

The study was approved by the Regional Committee for Medical and Health Research Ethics (2017/138) and by local data protection office at Oslo University Hospital (2017/467)

Results

Among 9311 subjects with type 1 diabetes, the mean age at onset was 8.8 years. At the end of follow-up, mean disease duration was 18.4 years (range 0.03 – 45.00) and mean age 27.1 years (0.8 – 59.5). The majority (88.5%) were born in Norway with two Norwegian born parents (Table 1). Matched controls had same sex, and county of birth and similar date of birth by design (Table S1).

Incidence and risk factors for ESRD

During 170,945 person years of follow-up, 130 developed ESRD (Fig. 1). The probability of developing ESRD in patients with type 1 diabetes was 0.7% (95% CI 0.4% – 0.9%) after 20 years and 5.2% (95% CI 4.3% - 6.2%) after 40 years of diabetes duration (Fig. 2). Among matched controls, 31 developed ESRD, and the hazard ratio for ESRD in type 1 diabetes vs. controls was 35.5 (95% CI: 23.1 – 54.6), and the probability of ESRD in controls were correspondingly low (Fig. 2). Probabilities of ESRD using traditional Kaplan-Meier failure estimates ignoring death as competing risk gave similar results, as shown in Figure S2.

Lower age at onset of type 1 diabetes was associated with significantly lower rates of ESRD, and there was a non-significant tendency towards a declining time trend (Table 2). The aHR for ESRD with higher education compared to lower education was 0.14 (95% CI 0.07 – 0.27) (Fig. 3 and Table 2).

ESRD was associated with four to five-fold higher rate of CHD compared to those who did not develop ESRD (aHR 4.53, 95% CI 3.04 –6.76, *P*-value < .001).

CHD as a risk factor for ESRD

A CHD event was documented in 3% (295/9311) of patients without known history of ESRD (Fig. 1, transition 3). Among the 295 patients, 13% (n = 38) later developed ESRD (Fig. 1, transition 4). CHD was associated with a 14-fold increased rate of ESRD (aHR = 14.3, 95% CI: 9.2 –22.2, Table 2) adjusting for sex, educational level, country of origin, age and calendar-year of diabetes onset.

Mortality and ESRD

Among the 130 type 1 diabetes patients who developed ESRD, 27% (35/130) died (71% male), compared to 3% (292/9181) in those without ESRD (Fig. 1). ESRD was associated with six-fold higher mortality rate (aHR 6.67, 95% CI 4.58 – 9.71) (Table S3).

Sensitivity analyses

Age at onset of type 1 diabetes was modelled as continuous variable in the main analysis, and we performed additional analyses where age was categorized into 0–9 years (early onset) and 10–14 years (late onset) for comparison with other studies. In order to develop ESRD, the aHR for onset at 10–14 versus 0–9 years was 1.45 (95% CI 1.02 – 2.07, *P*-value .04). We also performed the same analysis with age at diagnosis categorized into 0–4 (reference, aHR 1.0), 5–9 (aHR 1.53, 95% CI 0.84 – 2.76) and 10–14 years

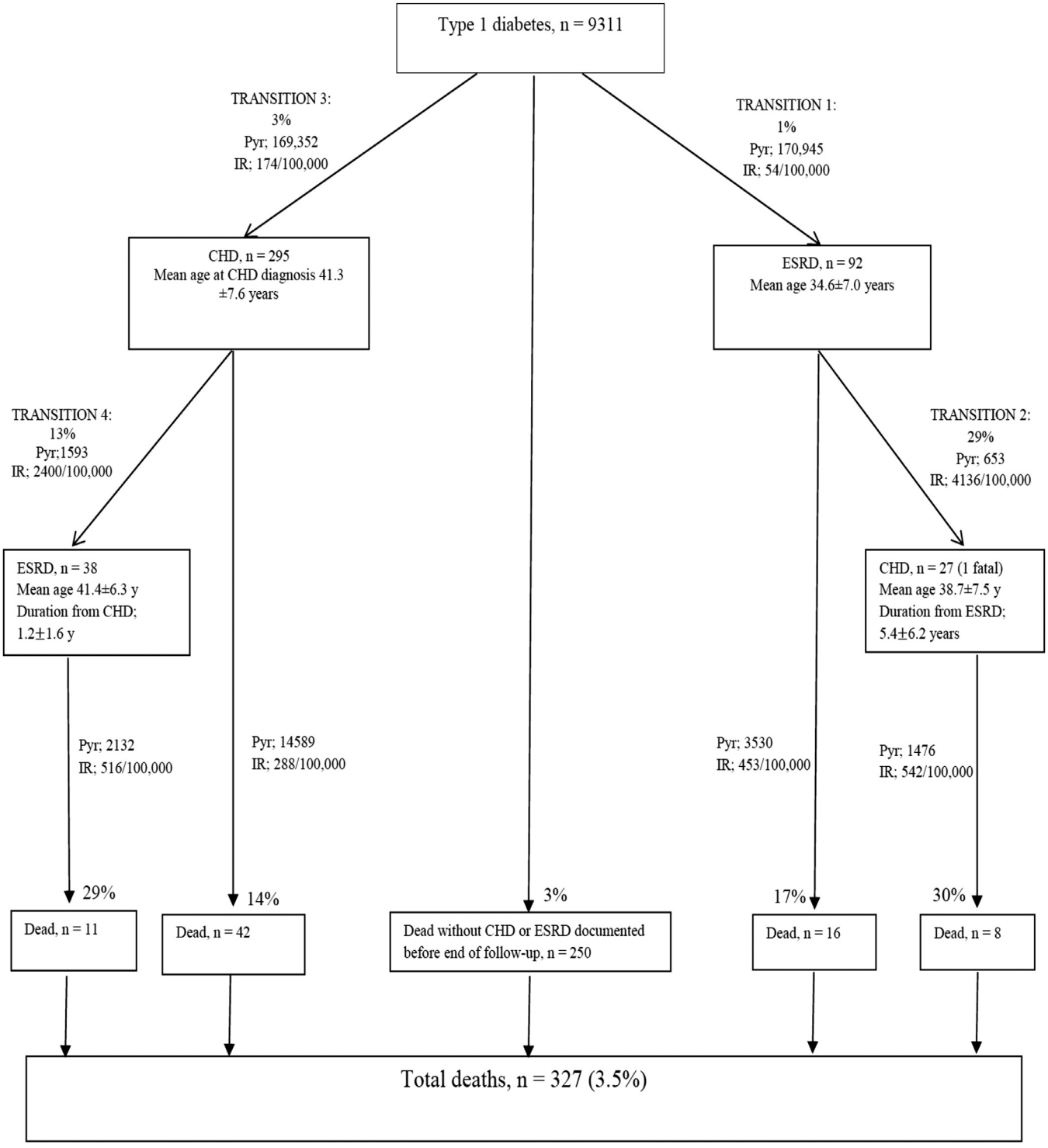

Fig. 1. Individual patient flow and events during follow-up. End-stage renal disease (ESRD), coronary heart disease (CHD), incidence rate (IR) and person years (Pyr).

(aHR 2.35, 95% CI 1.35 – 4.10). Probability of ESRD in subjects with type 1 diabetes by age at onset, is shown in supplemental material (Figure S3).

As our study cohort consists of many young subjects (mean age 27.1 years) with type 1 diabetes, additional sensitivity analyses were performed by excluding subjects who were diagnosed with type 1 diabetes in the earliest half of the period (before January 1, 1995), leaving 3088 subjects with type 1 diabetes for analysis. These contributed 101,922 person years, during which 124 (4%) developed ESRD. Mean diabetes duration and age at ESRD were both nearly the same as for the total cohort; 27.0 versus 26.5 years and 36.9 versus 36.5 years, respectively. The probability of developing ESRD in this sub-cohort by cumulative incidence function was also similar as for the total cohort; 0.8% versus 0.7% after 20 years and 5.3% versus 5.2% after 40 years of diabetes duration. Being diagnosed with CHD was associated with higher risk for ESRD, while

Table 2
Predictors of incident ESRD in patients with childhood-onset type 1 diabetes.

	Unadjusted HR (95% CI)	*P*-value	Adjusted HR* (95% CI)	*P*-value
Coronary Heart Disease†	19.9 (12.8 – 30.7)	<0.001	14.3 (9.2 – 22.2)	<0.001
Sex (female)	0.63 (0.44 – 0.90)	0.010	0.75 (0.52 – 1.07)	0.12
Age at onset of T1D (continuous)	1.10 (1.04 – 1.15)	<0.001	1.06 (1.01 – 1.12)	0.02
Lower education‡	1.0 (reference)		1.0	
Intermediate education	0.48 (0.33 – 0.68)	<0.001	0.54 (0.38 – 0.78)	0.001
Higher education	0.11 (0.06 – 0.21)	<0.001	0.14 (0.07 – 0.27)	<0.001
Calendar year of type 1 diagnosis (continuous)	0.982 (0.954 – 1.010)	0.20	0.987 (0.960 – 1.016)	0.39
Non-Norwegian§	1.19 (0.61 – 2.34)	0.62	1.02 (0.52 – 2.01)	0.95

* Hazard ratio (HR) estimated with Cox regression model and adjusted for all variables above,
† Coronary heart disease (CHD) modelled as a time-varying covariate: for each individual who developed CHD, the status changed from no CHD to CHD at diagnosis of first CHD event prior to ESRD.
‡ Lower education (compulsory, ≤ 10 years), Intermediate (11–13 years), Higher level (≥ 14 years),
§ If the individual and both parents were born in Norway, the individual is defined as Norwegian.

Table 3
Sensitivity analyses with subjects diagnosed with type 1 diabetes before 1995; predictors of incident ESRD (N = 124) in patients with type 1 diabetes (N = 3088).

Variables	Unadjusted HR* (95% CI)	*P*-value	Adjusted HR* (95% CI)	*P*-value
CHD†	19.3 (12.4 – 29.9)	<0.001	14.1 (9.0 – 22.0)	<0.001
Sex	0.60 (0.42 – 0.87)	0.007	0.73 (0.50 – 1.05)	0.09
Age at onset of type 1 diabetes (continuous)	1.09 (1.03 – 1.14)	0.001	1.05 (1.0 – 1.10)	0.06
Diagnosis year (continuous)	0.989 (0.957 – 1.023)		0.998 (0.964 – 1.031)	0.88
Lower education‡	1.0 (reference)		1.0 (reference)	
Intermediate education	0.49 (0.34 – 0.70)	<0.001	0.56 (0.39 – 0.81)	0.002
Higher education	0.10 (0.05 – 0.21)	<0.001	0.13 (0.07 – 0.27)	<0.001
Non-Norwegian§	0.86 (0.38 – 1.94)	0.71	0.71 (0.31 – 1.61)	0.41

* Hazard ratio by using Cox regression model,
† Coronary heart disease (CHD) modelled as time-varying covariate; for each individual who developed CHD, the status changed from no CHD to CHD at diagnosis of first CHD event prior to end-stage renal disease (ESRD).
‡ Lower education (compulsory, ≤ 10 years), Intermediate (11–13 years), Higher (≥14 years),
§ If the individual and both parents were born in Norway, the individual is defined as Norwegian.

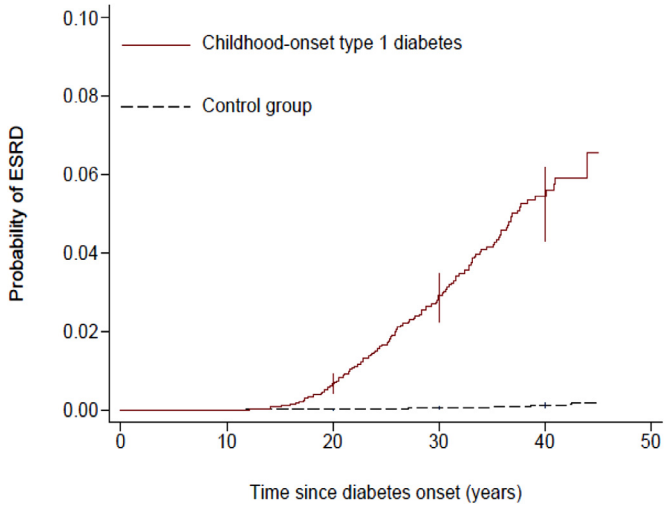

Fig. 2. Cumulative incidence of ESRD with death as competing risk. The vertical lines are the 95% confidence intervals. *Control group = sex- and age-matched without type 1 diabetes.

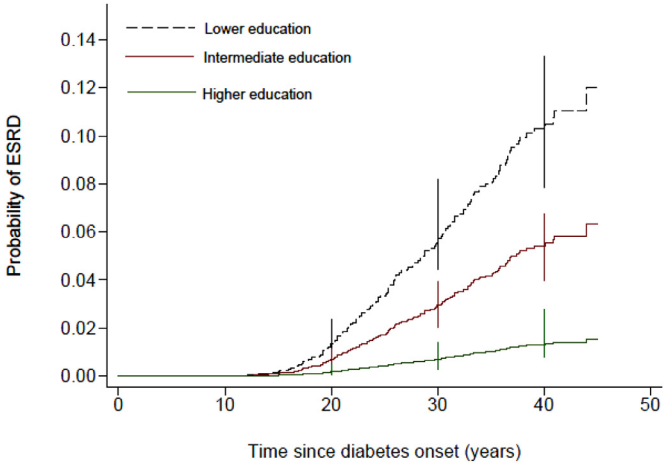

Fig. 3. Probability of ESRD by educational level*: shown by cumulative incidence function (with death as competing risk) The vertical lines are the 95% confidence intervals. *Lower education (compulsory, ≤10 years), Intermediate (11- 13 years), Higher (≥14 years).

lower age (continuous) at onset of type 1 diabetes and higher education (both "intermediate" and "higher" categories) were still the only covariates associated with significantly lower rate of ESRD (Table 3).

Discussion

Our major findings were: 1) The risk of ESRD was 35-fold higher in subjects with type 1 diabetes when compared to controls, 2) Higher education was associated with substantially lower risk of ESRD in subjects with type 1 diabetes, and 3) CHD was associated with a 14-fold higher rate of ESRD in subjects with childhood-onset type 1 diabetes.

Strengths and limitations

Among the strengths of this study is the nationwide, population-based, prospective design, long term follow-up, and linkage of several nationwide registries with high completeness using the unique personal identification number, and large sample

size allowing for precise estimates of the severe outcome ESRD. Another strength of this study is the low possibility of selection bias due to free access to a public health care system and essentially complete ascertainment of type 1 diabetes and ESRD.

A limitation is that we did not have access to clinical risk factors for ESRD such as HbA1c, blood pressure, lipid profile, body mass index and smoking. Another important limitation is we did not have the kidney function measurements during follow-up to assess the development of CKD to final ESRD. The definition of ESRD was based purely on the introduction of dialysis or kidney transplantation due to chronic renal failure. The information listed above is not possible to retrieve retrospectively for the whole population.

CHD was diagnosed in specialist health care, and we cannot exclude the possibility that some CHD were undiagnosed. The cohort is also relatively homogenous with largely Norwegian background. Therefore, our results may not be generalized to other countries and ethnicities. Some analyses have wide CI due to low number of cases and should be interpreted with caution.

Incidence of ESRD

We found low incidence of ESRD (5.2% after 40 years of diabetes duration) as expected and in line from an earlier study from Norway[4], but lower than reported from several other studies[3,17]. A systematic review reported in 2016 the 25-year cumulative incidence of ESRD range to be from 3.3% to 7.8%, whereas our estimates of 1.6% is even lower. They also report the relative risk to be between 6.2 and 12.0 in diabetic populations compared to non-diabetic [18]. But here they have not distinguished between type 1 and type 2 diabetes and the age group is older (≥30 years). However, both factors are important when estimating the risk for developing ESRD. The excessive risk in diabetic population is thus well-recognized, but there are no studies comparing young adult with type 1 diabetes and their risk of ESRD compared to a nationwide background population.

There was no significant decreasing risk of ESRD with time of type 1 diabetes diagnosis in our cohort. Although a decrease could have been expected based on other studies showing decreasing time trends in nephropathy [19], the lack of time trend in ESRD may be explained by the fact that our patients are still relatively young and progression from CKD to ESRD may take several years, often 10–15 years depending on the different stages and risk factors [20].

Educational level

We found substantially lower risk of ESRD with higher educational level, when compared to lower educational level, and the significant association is in line with the pattern seen in previous studies and for other diabetes complications [21,22]. The access to high-quality healthcare is equal for all inhabitants and free of charge in Norway. There were no significant differences regarding the proportions having low, intermediate and higher education in the cases compared to the control group. The explanation behind low education and high risk of ESRD are not known. We speculate that the highly educated may be in a better position to understand their disease execute self-care and thus good metabolic control. On the other hand, severe chronic kidney disease and other complications in early age may also limit the proportion taking higher education.

Association between ESRD and CHD

CHD is associated with lower glomerular filtration rate (GFR) both in the general population [23] and in patients with type 1 diabetes [24]. It is also well-known that nephropathy caused by hyperglycemia may result in ESRD and hence increases the risk of CVD, including myocardial infarction [25].

The association between CHD and CKD seems in many cases also to be connected to inflammation and atherosclerotic processes, which are found in both diseases [6]. Atherosclerosis is today seen as an inflammatory disease leading to CVD and CHD. Several interleukins, hs-CRP and TNF-α is also reported to be associated with reduced kidney function [26]. Mutual risk factors contributing to CVD in general and diabetic complications included CKD are showed by FinnDiane Study group [27]. In another study variability in HbA1c was predictive of both CVD and progression of renal disease [28].

Our study also confirms the high association between the two comorbidities where ESRD significantly increases the risk of CHD, and CHD increases the risk of ESRD. However, the most significant association was found to be the development of ESRD after CHD.

Role of sex, duration and age at onset of type 1 diabetes as risk factors for ESRD

After adjustment for the covariates, we found no significant association with sex and risk of ESRD, this is in accordance with other newer studies in those with diagnosed type 1 diabetes before 15 years of age [8,29].

In our study when age at onset of type 1 diabetes is modelled as a continuous variable, and divided into age groups, higher age at onset of type 1 diabetes was significantly associated with higher risk for development of ESRD (note that duration is inherently accounted for in the Cox model). This is generally in line with previous studies [30,31]. There are several hypotheses regarding the explanation for the association of higher age at diabetes onset (especially after the age of 10 years) with higher risk of ESRD: genetics, pubertal alteration in sex hormones and the diagnosis of a chronic disease during puberty with both physiological and psychological changes contributing to poorer glycemic control.

Implications

The incidence rate of ESRD in our study was lower than what has been reported from other studies of childhood-onset type 1 diabetes patients [3,20], but ESRD still represents a high disease burden in terms of quality of life, economy, morbidity and mortality for the patients, and also an economic burden for the society. Our results also highlight the importance of educational background of the subjects and the influence on the risk for complications, and the importance to take this in account both in pediatric and adult diabetes care.

CHD was associated with a 14-fold increased rate of subsequent ESRD and should lead to even tighter management of modifiable risk factors of both CHD and CKD. Intensive preventive intervention of CKD might also be protective of CHD, which in turn can reduce or delay the progression from CKD to final stage with ERSD.

Conclusion

In our nationwide study we found a low risk of developing ESRD in childhood-onset type 1 diabetes patients in Norway, but still almost 35-fold higher than in matched controls without type 1 diabetes. One out of three patients with ESRD developed CHD first, and CHD was associated with 14-fold higher risk for ESRD. Among subjects with type 1 diabetes, those with higher education had substantially lower risk of ESRD, when compared to those with lower education.

Author contributions

G.J, T.S., L.C.S and M.S. planned and conceptualized the project. M.S wrote the first draft of the manuscript and organized the data. M.S, L.C.S and G.T. analyzed the data. L.C.S supervised the analysis and interpretation of data. A.R. helped understanding the data from the Norwegian Renal Registry and transplantation data. T.J contributed with writing the section Discussion and provided literature. All authors critically reviewed, contributed to discussion and approved final version of the manuscript. M.S. had full access to all the data in the study and takes full responsibility for interpretation and accuracy of the data, and analysis.

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Data access

All data have been retrieved with approval from the Regional Committee for Medical and Health Research Ethics in Norway, Statistics Norway, Norwegian Childhood Diabetes Registry, CVDNOR Project, the Norwegian Patient Registry, The Norwegian Renal Registry and Norwegian Cause of Death Registry. All data are publicly available upon application with restrictions due to data protection and regulations.

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