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Prognosis for Type 1 Diabetes with Diabetic Nephropathy between 2000 and 2020 - Changes in Kidney Function Decline Over Time and Development of Cardiovascular Disease, Kidney Failure, and Mortality

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Introduction: Individuals with type 1 diabetes (T1D) and diabetic nephropathy (DN) experience progressive kidney function decline and high risk of cardiovascular disease (CVD) and mortality. This study explored changes in kidney function decline in new-onset DN between 2000 and 2020 and provided an updated prognosis for risk of kidney failure, CVD, and mortality.

Methods: This is a register-based cohort study in T1D with new-onset DN (severely increased albuminuria) between 2000 and 2020 at Steno Diabetes Center Copenhagen, Denmark. Data were derived from electronic health records and national registers. Kidney function development was expressed as trajectories of estimated glomerular filtration rate (eGFR) and measured GFR (mGFR) using mixed-effects models. The prognosis was presented in probabilities of developing complications, stratified by sex, prior CVD, and risk factor control by using simulations based on Poisson regression analysis.

Results: The cohort comprised 591 individuals with median (interquartile range [IQR]) age at DN onset of 53 (39–66) years and 57% were male. In 283 participants, mGFR were available. Plots of eGFR trajectories illustrated tendencies toward higher eGFR in more recent years; however, this was not confirmed in mGFR trajectories. Poor risk factor control, prior CVD, and male sex impacted mortality and morbidity rates negatively. For men and women with fair risk factor control and no prior CVD, the 10-year mortality rate from onset of DN was 28% and 26%, respectively. For men and women with poor risk factor control and CVD prior to DN onset, the 10-year-mortality rate was 62% for each sex.

Conclusion: The results do not support an improved prognosis for T1D and DN, emphasizing the urgent need for new therapeutic approaches.

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Diabetic kidney disease is a frequent and serious complication of diabetes[1] and it is the leading cause of chronic kidney disease and kidney failure in the USA, Denmark, and other developed countries.[2,3] Diabetic kidney disease is characterized by increased albuminuria and/or decreased kidney function with an eGFR $<$ 60 ml/min per 1.73 m^2. DN in this study is defined by severely increased albuminuria.[4]

Compared to the general population, individuals with T1D experience premature mortality, which primarily, is due to increased risk of CVD. Furthermore, individuals with concomitant kidney disease are particularly prone to CVD and premature mortality as albuminuria increases and kidney function decreases.[5-8]

Decades ago, clinical studies investigating interventions for T1D and DN demonstrated renoprotective effects of improved glycemic control,[9,10] blood

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pressure control,[11] and treatment with renin-angiotensin system (RAS) inhibitors.[12] Following this, decreasing incidence of DN have been reported[13,14] as well as a slower decline in eGFR. Survival rates have also improved compared to the grave natural progression of DN, with a mean survival of 5 to 7 years after diagnosis.[15-17] However, since the introduction of RAS inhibition in 1993, no novel treatments have emerged for the management of DN in T1D.

The aim of this register-based cohort study was to investigate whether the prognosis has improved further for individuals with T1D and new-onset DN between 2000 and 2020. We investigated the impact of calendar time on kidney function decline, assessed by trajectories of eGFR and mGFR and provided an updated prognosis for the development of CVD, kidney failure, and death in people with T1D and new-onset DN.

METHODS

Study Design and Population

This register-based cohort study comprised 591 individuals with T1D and DN attending the outpatient clinic at Steno Diabetes Center Copenhagen, Denmark between January 1, 2000, and December 31, 2020. T1D was defined either as age <30 years and insulin treatment at diabetes onset, or age ≥ 30 years and insulin treatment at diabetes onset combined with either nonfasting glutamic acid decarboxylase 65 antibody positivity or C-peptide value below the reference limit. DN was defined as diabetes with severely increased albuminuria (urine albumin excretion rate) $>$ 300 mg/24 h or urine albumin-to-creatinine ratio $>$ 300 mg/g) in 2 separate measurements at least 60 days apart. Baseline was set as the date of DN onset, which was defined as the date of the second measurement of severely increased albuminuria. Follow-up ended at time of death, emigration, or December 31, 2020, whichever occurred first.

Individuals with DN attending Steno Diabetes Center Copenhagen are offered annual examinations of mGFR. A subpopulation consisting of 283 individuals had available information on mGFR.

Ethics approval and participant consent are not required for register-based studies according to Danish law. Access and use of data were approved by the Danish Data Protection Agency and the Danish Patient Safety Authority.

Data Sources and Study Variables

Data were derived from electronic health records, the National Patient Register, Register of Medicinal Products, National Cause of Death Register, and the National Database for Biochemical Tests (LABKA). eGFR was calculated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration 2009 equation.[18] Creatinine assay was changed from modified Jaffe to isotope dilution mass spectrometry on September 1, 2004. Creatinine measurements before this date were transformed with the following equation: (non isotope dilution mass spectrometry creatinine (μmol/l−5.92)/1.065 prior to eGFR calculation.[19] Plasma clearance of chromium-51 labeled ethylenediamine tetra acetic acid was used for mGFR examinations.[20]

Drug exposure was defined as a minimum of 1 redeemed prescription during the previous year, derived from the Register of Medicinal Products. Information on smoking status, body mass index (BMI), age at diabetes onset, systolic and diastolic office blood pressure, and retinopathy status (none, no proliferative, and proliferative) was derived from electronic health records.

If baseline variables were not available at the time of DN onset, the closest measurement in time was used, which did not exceed 1 year prior to or 4 months after date of DN onset. Urine albumin-to-creatinine ratio and urine albumin excretion rate were combined into 1 new variable, albuminuria. To account for variability in blood pressure and albuminuria, we calculated the mean of all measurements for a person from 1 year prior to and 1 month after the baseline date.

All available serum creatinine measurements during follow-up were included. For all other follow-up variables, the most recent measurement prior to each creatinine value was used, not exceeding a time span of 1 year.

The following threshold values were applied for categorizing fair or poor risk factor control: HbA_{1c} 60/75 mmol/mol, systolic blood pressure 130/150 mm Hg, low density lipoprotein (LDL)-cholesterol 2.0/4.0 mmol/l, triglyceride 1.5/3.0 mmol/l, and albuminuria 300/1000 mg/g or mg/24 h.

End Point Definition

Diagnosis and procedure codes were derived from the National Patient Register. CVD was defined as the date of the first occurrence of a diagnosis or procedure code for the following: stroke, acute myocardial infarction, ischemic heart disease, heart failure, coronary artery bypass surgery, or percutaneous coronary intervention (applied codes are specified in the Supplementary Methods).

Kidney failure was defined as the date of the first occurrence of either a diagnosis or procedure code for dialysis treatment, kidney transplantation, or kidney failure, or for the occurrence of eGFR $<$ 15 ml/min per 1.73 m^2 based on at least 2 separate serum creatinine measurements with minimum 60 days apart.

Statistical Analysis

Data were reported as median (IQR) for continuous data and count and percentages for categorical data. Two-sided tests and a significance level of $P < 0.05$ were applied. Logarithmic transformation was performed based on distribution and the relationship between the independent and dependent variables. For clinical interpretation decadic logarithm was chosen for albuminuria.

The eGFR trajectories were estimated separately for men and women, using mixed effects models. Fixed effects in the models included age, natural cubic splines of the date of DN onset and DN duration, and interaction terms between the splines; random effects of person and random slopes of DN duration were also included. Models adjusted for clinical measurements included the following fixed effects in addition to the aforementioned: albuminuria; HbA_{1c}; hemoglobin; LDL-cholesterol; triglyceride; systolic blood pressure; BMI; and exposure to RAS inhibitor, antihypertensive, and lipid-lowering medication. For illustration, 4 trajectories were estimated for date of DN onset in the calendar years 2000, 2005, 2010, and 2015.

To illustrate the rates of kidney failure, CVD, and mortality, we presented the data in a multistate model. The model consisted of 8 states in total, 4 of which were disease categories for the following: (i) DN only, (ii) CVD, (iii) Kidney failure, and (iv) CVD + kidney failure; and 4 categories for death from each of the preceding disease states. All individuals entered the model in either the DN-only state or CVD-state, depending on whether CVD was present prior to baseline. Depending on the development of CVD, kidney failure and death, the individual then progressed through the different states of the model. All deaths were accounted for regardless of the cause. The states of death were not based on the cause, but on presence of the condition (CVD, kidney failure, or both) prior to or at time of death. As an example, a person recorded as having both CVD and kidney failure, who then died, would be in the CVD + kidney failure state of death, regardless of whether death was related to these conditions.

Follow-up time was split into 2-month intervals to ensure proportional hazards; and age, diabetes duration, and DN duration were computed at the beginning of each interval. Person-years in each state were calculated along with transition rates between the states.

Each transition was modelled using Poisson regression with adjustment for sex, age, DN duration, eGFR, albuminuria, HbA_{1c}, hemoglobin, LDL-cholesterol, triglyceride level, systolic blood pressure, and BMI. Using these models, we simulated the transitions in 8 different scenarios, 5000 simulations each. The different scenarios were all possible combinations of sex (men or women), risk factor control (fair or poor), and prior CVD or lack thereof. From the simulation results, probabilities of being in different states during the time after DN onset were calculated.

Missing data in the multistate analysis were managed by using multiple imputations by chained equations[21] implemented in the R package "mice".[22] By creating multiple predictions for each missing variable, this method accounts for the uncertainty of the imputation. Using multiple imputations by chained equations relies on the assumption that the data are missing at random. Predictive mean matching was applied to impute missing baseline values for all variables for all individuals. By running the multiple imputations by chained equations algorithm for 20 iterations each time, 20 complete data sets were created. The analysis, as described above, was run separately on each data set and then combined by Rubin's rules.[23] Predictions of transitions between states were calculated by using the "combine, then predict" method,[24] that is, the predictions were made only once after combining the modelling results. The applied analyses are described in detail in the Supplementary Methods.

RESULTS

There were 591 individuals with DN onset during follow-up. Baseline characteristics are shown in Table 1. Median (IQR) age at diagnosis of T1D was 23 (12–37) years, the median (IQR) age at DN onset was 53 (39–66) years and 337 (57 %) were male. At baseline, 73% received RAS inhibitor medication, 85% received antihypertensive medication (including RAS inhibitors) and 46% received lipid-lowering medication. The baseline median (IQR) albuminuria level was 505 (376–857) mg/g or mg/24 h. There were 6293 eGFR measurements in total, with a median (IQR) number of eGFR measurements of 7 (3–16) per person and a median (IQR) follow-up time of 4.9 (1.8–10.0) years.

Trajectories of eGFR

Adjusted eGFR trajectories for men and women with DN onset at age 53 years are shown in Figure 1 and the corresponding values are shown in Supplementary Table S1. Compared to women, men had higher eGFR levels at the time of DN onset but showed faster decline for all calendar years throughout follow-up. For DN onset in 2000, eGFR levels were lower at the time on DN onset and throughout follow-up for both men and women. The trajectories for DN onset in 2000 was approximately linear. The trajectories for 2005 to 2015 showed a faster decline during the first 5 years after DN onset, declining approximately 3.5 ml/yr for women

Table 1. Baseline characteristics

Demography	
Number of participants	591
Male sex, *n* (%)	337 (57)
BMI, median (IQR), kg/m^2	25.1 (22.2–28.0)
Smoking status, *n* (%)	
Yes	235 (40)
No	232 (39)
Missing	124 (21)
Medical history	
Age at diabetes onset, median (IQR), yrs	23 (12–37)
Age at DN onset, median (IQR), yrs	53 (39–66)
Diabetes duration, median (IQR), yrs	24 (17–36)
Retinopathy status, *n* (%)	
None	83 (14)
Nonproliferative	321 (54)
Proliferative	91 (15)
Missing	96 (16)
RAS inhibitor medication, *n* (%)	432 (73)
Any hypertensive medication, *n* (%)	505 (85)
Lipid-lowering medication, *n* (%)	273 (46)
Laboratory values	
Albuminuria, median (IQR), mg/g or mg/24 h	505 (376–857)
HbA_{1c}, median (IQR), mmol/mol	73 (63–85)
Hemoglobin, median (IQR), mmol/l	8.3 (7.5–9.0)
LDL-cholesterol, median (IQR), mmol/l	2.5 (1.9–3.3)
HDL-cholesterol, median (IQR), mmol/l	1.5 (1.2–1.9)
Triglyceride, median (IQR), mmol/l	1.3 (0.9–1.9)
Blood pressure, median (IQR), mm Hg	
Systolic	142 (129–156)
Diastolic	80 (72–87)

BMI, body mass index; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; mGFR, measured glomerular filtration rate; RAS, renin-angiotensin system.
Data are expressed as median (IQR) or numbers (frequency) as appropriate.

and 4.0 ml/yr for men. Five years after DN onset, the rate of decline seemed to attenuate for the same trajectories.

If we ignored the nonlinear trajectories shown in Figure 1, and calculated mean slopes for eGFR decline throughout follow-up, women had steeper decline in eGFR with later (calendar year) DN onset from a decline of 2.1 ml/yr in 2000, over 2.6 ml/yr in 2010, and to 3.6 ml/yr in 2015. For men, the eGFR decline was lower with later DN onset, with a decline of 3.2 ml/yr for 2015, 2.8 ml/yr for 2010, and 3.6 ml/yr for 2000.

In Figure 2, we show the effect of baseline and follow-up variables on eGFR levels. At baseline, higher age, albuminuria, and treatment with antihypertensive medication were associated with lower eGFR levels. Higher hemoglobin and HbA_{1c} (men only) were associated with higher eGFR at baseline. During follow-up, higher age, LDL-cholesterol (men only), BMI (men only), treatment with antihypertensive (men only) and lipid lowering medication were associated with lower eGFR. Higher albuminuria (men only), hemoglobin, LDL-cholesterol (women only), and systolic blood pressure were associated with higher eGFR levels.

Trajectories of mGFR

Trajectories of mGFR were estimated in 283 individuals, baseline characteristics are shown in Supplementary Table S2. This subpopulation was overall comparable to the total study population. However, compared to the total study population, the subpopulation was younger at diabetes onset with median (IQR) age of 17 (10–31) years versus 23 (13–37) years, had earlier DN onset with median age of 50 (38–57) years versus 53 (39–66) years and more were treated with RAS inhibitor at baseline (235 [83%] vs. 432 [73%]). The median (IQR) follow-up time was 5.3 (1.8–8.7) years. The adjusted mGFR trajectories are shown in Supplementary Figure S1 and the corresponding values in Supplementary Table S3. There was no apparent improvement in mGFR trajectories during the years 2000 to 2020.

Development of CVD, Kidney Failure, and Death

The median (IQR) follow-up time for development of complications was 7.1 (3.0–12.2) years. The multistate model, with person-years spent in each disease state and transition rates between the states, is shown in Figure 3. The development of CVD, kidney failure, and particularly both, increased mortality rate. The crude mortality rate (per 100 person-years) increased with development of complications: DN only: 2.4, kidney failure: 7.2, CVD: 9.2, and CVD + kidney failure: 18.7. CVD prior to DN onset had a high impact on the transition rates. The risk of developing kidney failure within the follow-up time was increased by 71% (95% confidence interval: 11%–163%) in persons with prior CVD compared to those without. Likewise, prior CVD increased the risk of death by 112% (57%–187%) for persons without kidney failure and by 98% (6%–269%) for persons with kidney failure, compared to those without prior CVD.

Out of the 102 individuals who developed kidney failure, 25 (25%) received a kidney transplantation during follow-up. Out of these, less than 3 received a combined kidney and pancreas transplantation (numbers < 3 cannot be reported due to data protection legislation). Five of the 25 kidney transplant recipients (20%) and 54 of the 77 nonrecipients (70%) died within follow-up.

We estimated the probability of developing CVD, kidney failure, and death depending on sex, prior CVD, and risk factor control. In Figure 4, we show the cumulative probability of being in different disease states during 10 years after DN onset estimated for a person with onset of DN at age 53. The corresponding values are shown in Supplementary Table S4 and Table S5. For men without prior CVD and with fair risk factor control, the mortality risk was 28% after 10 years, and the

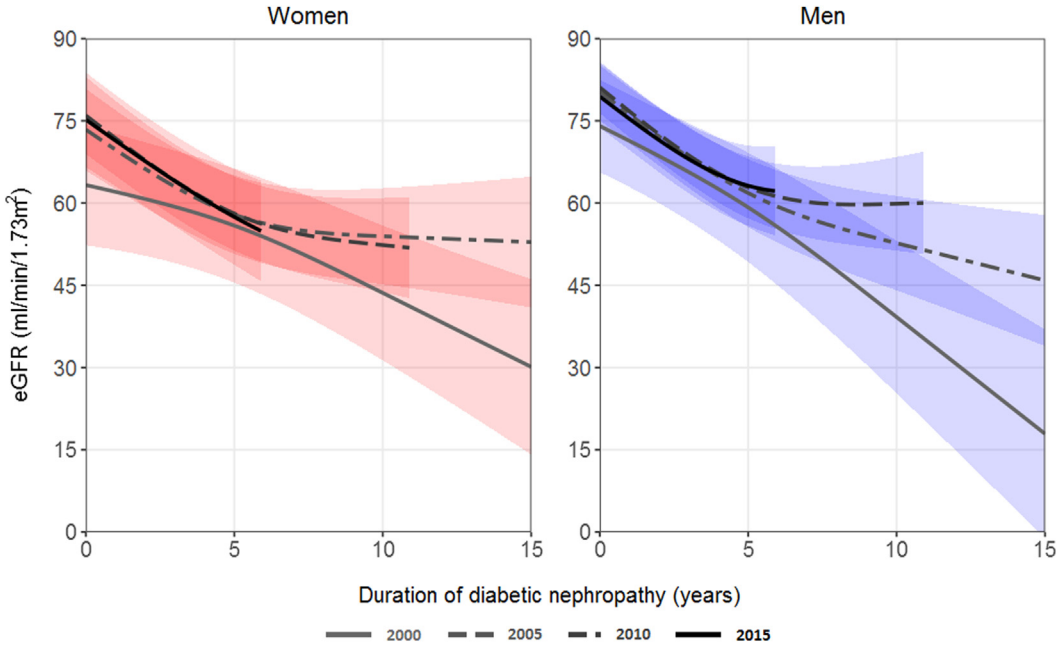

Figure 1. Development in eGFR trajectories after DN onset between 2000 and 2020. Estimated eGFR trajectories for women (red) and men (blue) with DN onset at age of 53 years in 2000 (solid grey line), 2005 (dashed line), 2010 (dashed dotted line) and 2015 (black solid line). The depicted trajectories are from the adjusted model with the following median baseline values: albuminuria (454 mg/g or mg/24 h); $HbA1_c$ (75 mmol/mol); hemoglobin (8.2 mmol/l); LDL-cholesterol (2.5 mmol/l); triglyceride (1.2 mmol/l); systolic blood pressure (142 mm Hg); BMI (25 kg /m^2); and exposure to RAS inhibitor, antihypertensive, and lipid-lowering medication. DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate in ml/min per 1.73 m^2.

probability of being alive without developing CVD or kidney failure was 47%. In case of poor risk factor control, the mortality risk was 44% and there was a 34% probability of being alive without CVD or kidney failure. For men with CVD prior to DN onset and poor risk factor control, the estimated mortality risk after 10 years was 62%. For women without prior CVD and fair risk factor control, the mortality risk was 26% and the there was a 59% probability of being alive without developing CVD or kidney failure. In case of poor risk factor control, the mortality risk was 40% and there was a 45% probability of being alive developing without CVD or kidney failure. For women with CVD prior to DN onset and poor risk factor control, the mortality after 10 years was 62%.

DISCUSSION

In this register-based cohort study including individuals with T1D and DN, we examined prognosis after onset of DN in relation to kidney function decline and development of CVD, kidney failure and death. Five years after DN onset, eGFR trajectories pictured a tendency toward an attenuated decline in more recent calendar years. However, the loss of kidney function was still substantial over time. We were not able to confirm the attenuation of eGFR decline after 5 years in the subpopulation with more precisely mGFR, using isotope plasma clearance technique. The risk of developing CVD, kidney failure, and death were high and was impacted negatively by male sex, prior CVD, and poor risk factor control.

Improved GFR trajectories after implementation of glucose-lowering and blood pressure lowering treatments, including RAS inhibitors have previously been shown.[16,17,25] In a previous publication from our group, Andrésdóttir *et al.*[17] found annual mGFR decline of 3.3 ml/min per 1.73 m^2 between 2000 and 2010, which was an improvement compared to a cohort from 1983 to 2000[16] with an annual decline of 4.0 ml/min per 1.73 m^2. Both studies included individuals with T1D and DN, regardless of time of DN onset. The inclusion periods overlap between the current cohort and the cohort from Andrésdóttir *et al.*;[17] and therefore, some participants were included in both studies. We could not demonstrate further improvement in the decline of kidney function over the last 2 decades.

The higher eGFR at time of DN onset, could potentially be an effect of renoprotective therapy, (RAS inhibitor medication) initiated in individuals with moderately increased albuminuria, succeeding in decelerating kidney function loss. The time of DN onset was based on available albuminuria measurements in the laboratory history. Individuals with a true onset of DN earlier than detected in this study could affect the results. It is likely that the frequency of this occurring

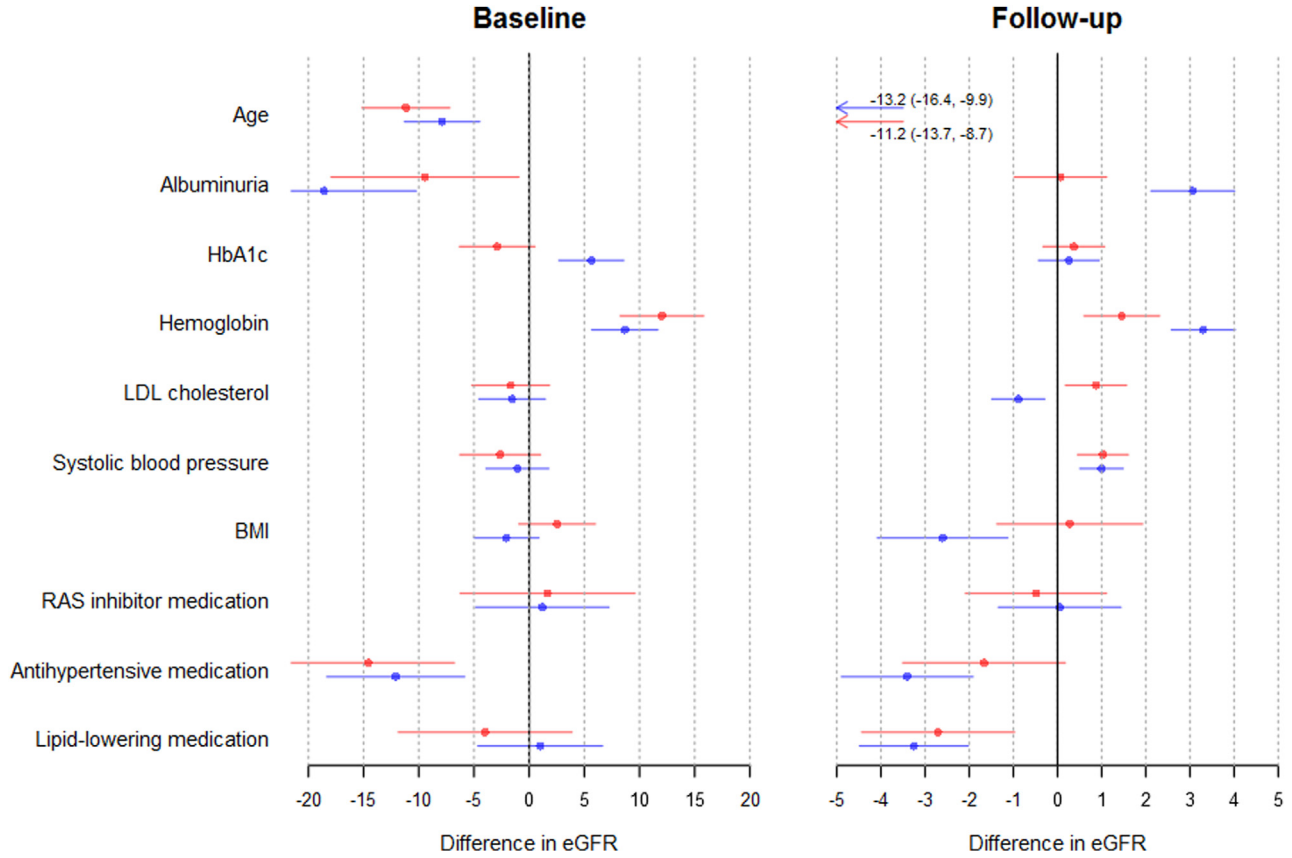

Figure 2. Effect on eGFR level by clinical characteristics. Adjusted effect on eGFR level of 1 SD change (or doubling of albuminuria) in baseline and follow-up variables. Red: women, blue: men. Baseline SD values: age 16.6 years, HbA_{1c} 18.1 mmol/mol, hemoglobin 1.1 mmol/l, LDL cholesterol 1.1 mmol/l, systolic blood pressure 22 mm Hg, and BMI 4.5 kg/m^2. Follow-up SD values: age 14.4 years, HbA_{1c} 16.8 mmol/mol, hemoglobin 1.1 mol/l, LDL cholesterol 0.9 mol/l, systolic blood pressure 21 mm Hg and BMI 4.7 kg/m^2. BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate in ml/min per 1.73 m^2; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; RAS, renin-angiotensin system.

is higher for individuals with DN onset in 2000 than at later calendar time due to availability of laboratory data. Another explanation could be earlier diagnosis; however, the screening process at our institution has not changed.

The eGFR trajectories imply a nonlinear decline with 2 segments, one for the first 5 years after DN onset with a more rapid decrease, and another segment for >5 years after DN onset picturing deceleration. Evidence suggests that the pattern of eGFR decline is not a progressive linear decline, as seen in the natural course of untreated DN in T1D, but rather that several more individual patterns exist.[26] The decelerating eGFR decline after 5 years could be impacted by individuals with a very rapid eGFR decline only contributing to the initial part of the trajectories after DN onset.

We did not find any significant effect of calendar time on the mGFR trajectories. The subpopulation included in the analyses of mGFR was comparable to the total population, besides slightly earlier diabetes and DN onset. There are limitations of using eGFR at the individual level and especially with eGFR > 60 ml/min per 1.73 m^2, however it is considered reliable, when applied at the population level.[27] The mGFR trajectories add evidence for an unchanged GFR trajectory over the past 20 years.

Individuals with T1D and DN are at increased risk of kidney failure, CVD, and early mortality. Because a significant number of people may pass away before developing kidney failure, premature death should be considered when assessing the risk of kidney failure.[28] To study the progression of DN while accounting for these competing risks, a multistate model was employed. In a similar study from our group as previously described, Andrésdóttir *et al.*[17] utilized data from Steno Diabetes Center Copenhagen spanning the years 2000 to 2010. Compared to this previous cohort, we reported higher transition rates to CVD (3.8 vs. 2.8) and higher mortality rates for both participants with DN only (2.5 vs. 1.4), CVD (9.2 vs. 5.1) and kidney failure (7.2 vs. 5.6). However, the transition rate to kidney failure was lower in the current study (2.0 vs. 3.7). Somewhat different criteria were employed in the previous study: the kidney failure end point included doubling of serum creatinine, and the participants did not necessarily have new-onset-DN; therefore the population had longer DN duration at

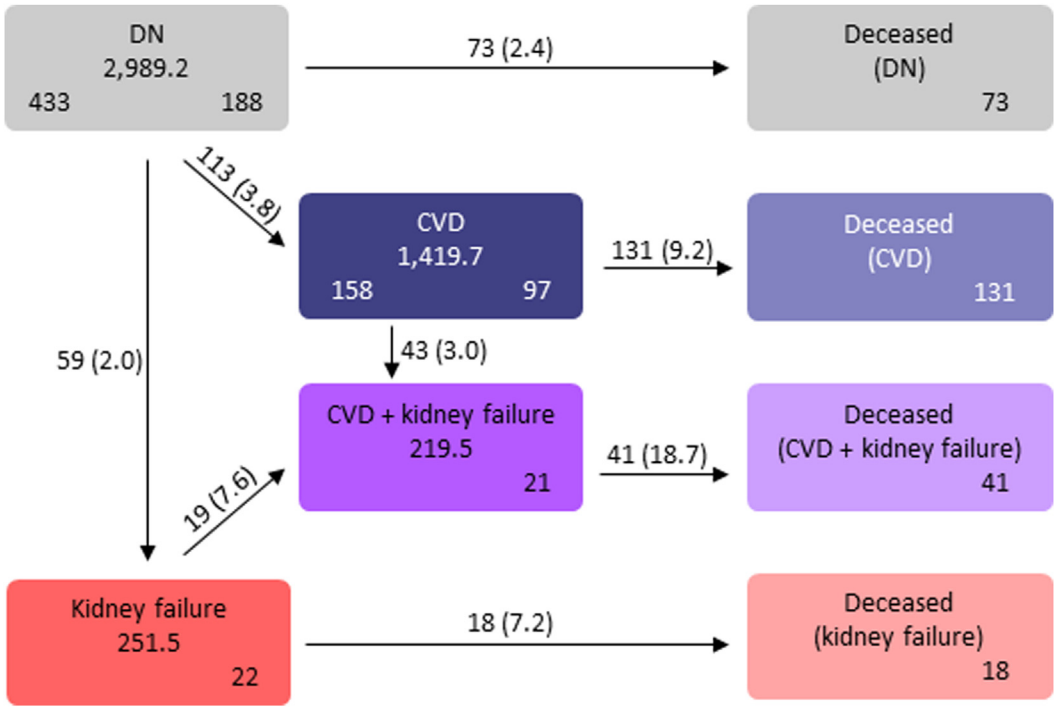

Figure 3. Multistate model. Disease states and transitions between states. Box numbers indicate the following: centered, person-years spent in this state; bottom-left, number of persons starting follow-up in this state; bottom-right, number of persons ending follow-up in this state. Arrow numbers indicate transitions (rate per 100 person-years). CVD, cardiovascular disease; DN, diabetic nephropathy.

baseline. In the current study, we followed-up with individuals from onset of DN whereas in the previous cohort they had a median DN duration at baseline of 8 years.[17] The different definitions of kidney failure could, at least partially, account for the lower transition rate to this state. There are discrepancies in how the incidence of kidney failure in DN have changed during recent times; some have indicated an increase,[29] others a stable incidence,[2,14,30] and some a decrease.[1,31-33] The discrepancy could, to some extent, be related to nationality and ethnicity of the populations,[34] and the pre kidney failure mortality has high impact on these incidence rates. Skupien *et al.*[35] described lower rate of kidney failure at Steno Diabetes Center Copenhagen compared to cohorts from USA and Finland, but at the same time higher mortality. At least in Denmark, despite reports showing decreased incidence of DN, we do not see a decrease in kidney failure onset.[2,13,30] Kidney transplantation improves morbidity and mortality risk.[36] This was not accounted for in the analyses. Of the 102 individuals developing kidney failure during follow-up, 25 (25%) had a kidney transplantation either at the time of kidney failure or after the diagnosis. Our analyses might therefore underestimate the risk of being in the kidney failure state without a kidney transplantation.

Despite decreasing incidence of CVD and mortality in individuals with T1D and DN, the rates remain severely increased compared to the general population.[37,38] Although a direct comparison to our previous study[17] is not possible, the increased mortality rates and higher transition rates to CVD indicate that the prognosis has not improved further during the past 2 decades. Our results demonstrate that prior CVD, male sex, and poor risk factor control continue to increase the risk of developing complications, as has been previously described.[17,29] The mortality and morbidity rates are high despite of fair risk factor control.

A strength of this study is the well-described cohort from a single center. Majority of individuals with T1D in the Capital Region of Denmark receive care at Steno Diabetes Center Copenhagen and therefore the cohort is representative of this population and minimizes selection bias. However, the single-center study also affects the generalizability of the findings to both populations with different characteristics and to different health care approaches.

The results represent individuals with T1D and severely increased albuminuria, because we have not included individuals without albuminuria, with moderately increased albuminuria, or with chronic kidney disease based on eGFR $<$ 60 ml/min per 1.73 m^2 solely,[39] which limits the generalizability of the results to other populations, including individuals with type 2 diabetes. Another limitation of the study is the register-based design, which can affect the reliability of the data and introduce biases. Data were based on national registers and electronic health records collected in a real-world setting, which can lead to incomplete and

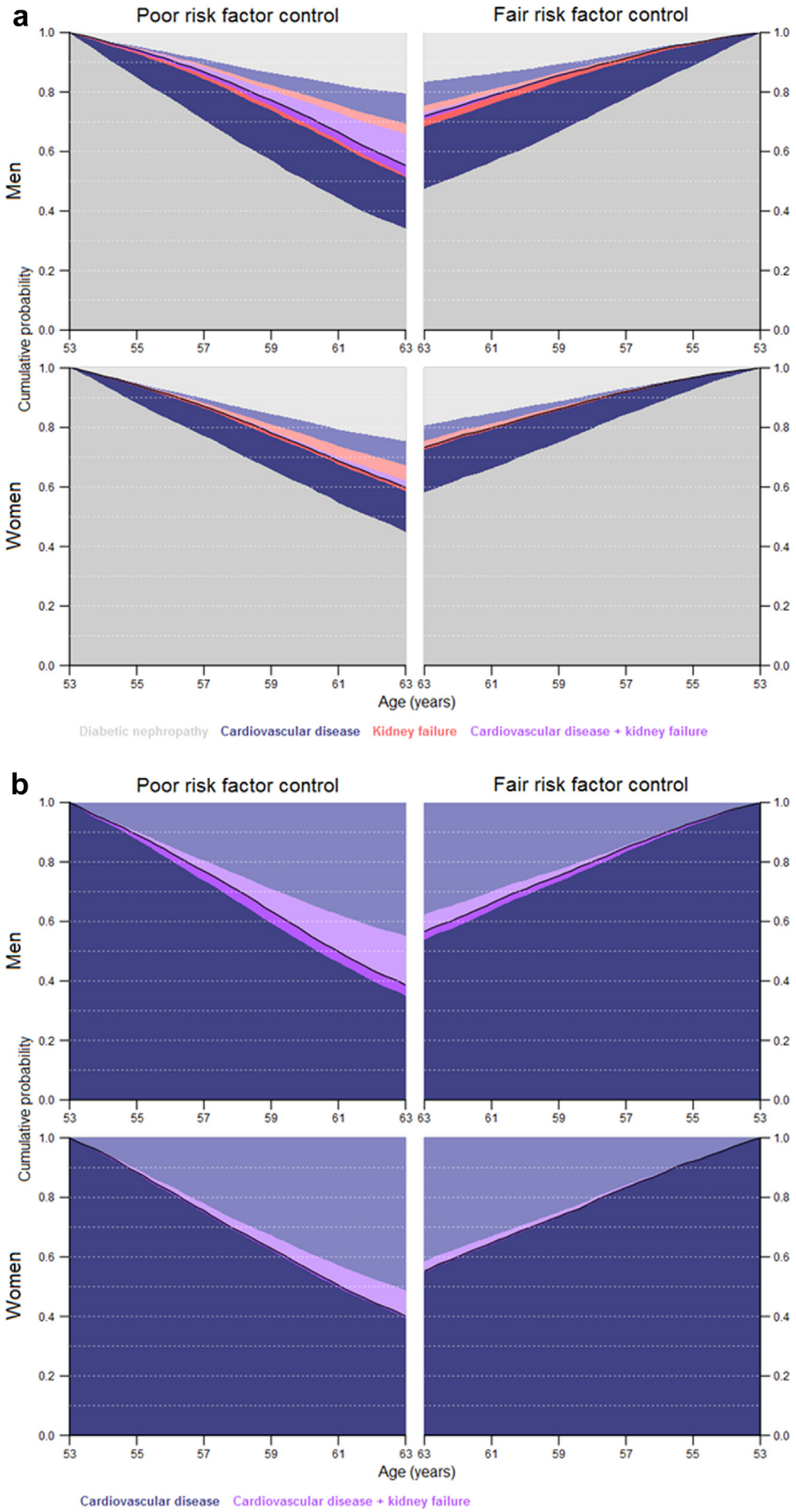

Figure 4. Risk of kidney failure, cardiovascular disease, and mortality after DN onset. Estimated probabilities of being in different states for a person with type 1 diabetes and with onset of diabetic nephropathy at age 53 years. (a) No prior cardiovascular disease. (b) Cardiovascular disease prior to onset of DN. Bright colors: black line, survival curve; grey, diabetic nephropathy; blue, cardiovascular disease; red, kidney failure; and purple, cardiovascular disease + kidney failure. Shaded colors above the survival curve are corresponding death states. Values for fair or poor risk factor control: HbA_{1c} 60/75 mmol/mol, systolic blood pressure 130/150 mm Hg, LDL cholesterol 2.0/4.0 mmol/l, triglyceride 1.5/3.0 mmol/l, and albuminuria 300/1000 mg/g or mg/24 h. In addition, the following values were used for both fair and poor risk factor control: diabetes duration: 25 years, eGFR 70 ml/min per 1.73 m^2, hemoglobin 8 mmol/l, and BMI 22 kg/m^2. BMI, body mass index; DN diabetic nephropathy.

inaccurate data. End point definitions were based on procedure and diagnosis codes. These can be erroneous or missing leading to misclassification. Missing data were handled under the assumption that data were missing at random, we found no clear indications that the missingness was related to unobserved factors. Particularly, retinopathy and smoking status had missing data, and these variables were not included in the models.

In this study, DN was diagnosed based on laboratory measurements of severely increased albuminuria. However, a kidney biopsy would be necessary to confirm a definitive diagnosis of DN. Although urine samples were part of regular consultations at the outpatient clinic, the diagnosis of DN relied on provision of urine samples, which could affect the time-point of DN onset. The frequency of urine analyses in the study cohort was stable during follow-up; therefore, we consider that the inaccuracy in time of DN onset has not biased the analyses of calendar time. Studies have indicated that the regression of albuminuria can lead to an improved prognosis.[40,41] We did not investigate the impact of albuminuria changes over time in this study.

The creatinine assay was changed in 2004. We attempted to minimize bias due to this by transforming previous creatinine measurements as described in the methods-section. BMI was used for adjustment for obesity; however, more accurately, central or visceral obesity is associated with progression of kidney disease. Measures of central obesity were unfortunately not available from the electronic health records.

In conclusion, for individuals with T1D and new-onset DN, we demonstrated a tendency toward an effect of later calendar times, with higher eGFR levels and attenuating eGFR decline beginning 5 years after DN onset. However, this was not confirmed in the mGFR trajectories. The GFR decline and the risk of kidney failure, CVD, and premature death continue to be substantial for individuals with T1D and DN.

The emergence of novel treatments such as sodium-glucose-cotransporter-2 inhibitors, glucagon-like peptide-1 agonists, and nonsteroidal mineralocorticoid receptor antagonists has generated high hopes for enhancing the prognosis of individuals with type 2 diabetes and chronic kidney disease.[42–45] There are currently no encouraging breakthroughs in treatments for DN in T1D. This study underscores the urgent need for further research in both cardiovascular and reno-protective therapies in T1D with DN.

DISCLOSURE

PR has received institutional grants from Bayer, Novo Nordisk, and AstraZeneca; consulting fees from Abbott, Astra Zeneca, Boehringer Ingelheim, Bayer, Novo Nordisk, Gilead, Sanofi Aventis, and Eli Lilly (honoraria to institution). DV received grants from Bayer A/S, Sanofi Aventis, Novo Nordisk A/S, and Boehringer Ingelheim. FP has received consulting fees from Astra Zeneca, Boehringer Ingelheim, and Novo Nordisk; and has received lecture fees from Astra Zeneca, Boehringer Ingelheim, and Novo Nordisk. MFM has received lecture fees from Novartis, Sanofi, and Boehringer Ingelheim. DV was until April 2023 Chair of the Steering Committee of the European Diabetes Epidemiology Group. DV, BC, and TWH owns stock or stocks options in Novo Nordisk A/S. DV is currently employed at Novo Nordisk A/S. All the other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The study is based on data from several Danish nationwide registers. All data in the register are stored and kept at Statistics Denmark (project number 707655). Register data are protected by the European and Danish Law and are not publicly available. Data can be accessed through application to the Danish Data Protection Agency and the Danish Health Authority.

AUTHOR CONTRIBUTIONS

Conceptualization and methodology were by CGP, KJ, BC, MFM, TWH, FP, DV, and PR; Formal analysis and data curation were done by KJ. Visualization was by KJ and CGP. Writing of the original draft was by CGP. Writing review and editing were by CGP, KJ, BC, MFM, TWH, FP, DV, and PR. Supervision was by PR, FP, and DR. Project administration and funding acquisition were by CGP.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References

Figure S1. Development in mGFR trajectories after DN onset between the years 2000 and 2020.

Table S1. Predicted values for eGFR trajectories depicted in Figure 1.

Table S2. Baseline characteristics.

Table S3. Predicted values for mGFR trajectories depicted in Figure S1.

Table S4. Estimated probabilities of developing complications depicted in Figure 4a.

Table S5. Estimated probabilities of developing complications depicted in Figure 4b.

STROBE Checklist.

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