Development of Microvascular Complications and Effect of Concurrent Risk Factors in Type 1 Diabetes: A Multistate Model From an Observational Clinical Cohort Study

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OBJECTIVE

Type 1 diabetes is a complex disease, and development of multiple complications over time can be analyzed only with advanced statistical methods. This study describes the development of microvascular complications and explores the effect of complication burden and important concurrent risk factors by applying a multistate model.

RESEARCH DESIGN AND METHODS

We used a clinical cohort at the Steno Diabetes Center Copenhagen to study the development of diabetic kidney disease, retinopathy, and neuropathy. We extracted information from electronic patient records and estimated incidence rates of complications by concurrent complication burden. We explored the extent to which concurrent complications modify the effect of selected risk factors on the development of microvascular complications.

RESULTS

We included 3,586 individuals. Incidence rate ratios in individuals with two previous complications were 3.2 (95% CI 2.3–4.5) for diabetic kidney disease, 2.1 (1.5–3.1) for retinopathy, and 1.7 (1.2–2.4) for neuropathy compared with individuals without complications. The models included diabetes duration; calendar time and age as timescales; and sex, HbA_{1c}, lipid-lowering and antihypertensive treatment, systolic blood pressure, BMI, estimated glomerular filtration rate (eGFR), cardiovascular disease (CVD), LDL cholesterol, insulin dose (units/kg/day), and smoking status as covariates. Effects of HbA_{1c}, diabetes duration, systolic blood pressure, BMI, eGFR, and LDL cholesterol where not modified by concurrent complication burden, whereas the effect of sex and CVD were.

CONCLUSIONS

The risk of microvascular complications highly depends on the concurrent complication burden and risk factor profile in individuals with type 1 diabetes. The results emphasize attention to risk factors, regardless of existing number of complications, to prevent development of further microvascular complications.

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The prevalence of type 1 diabetes has increased over the past decades (1,2). Increased life expectancy means that people live longer with diabetes (3–5); thus, potentially more years are lived with both macrovascular and microvascular complications (6,7). Type 1 diabetes is a complex disease, which develops in various complication states, and co-occurrence of multiple microvascular complications frequently is seen (8). So far, most studies are of a single complication, and the association between the worsening of one complication and the incidence of another is well described, although independently of other complications (9,10). At the same time, a sizeable group of individuals seems to be protected from microvascular complications (11–14), and some live several decades with type 1 diabetes without developing complications. Advanced statistical models, such as multistate models, offer an opportunity to explore the transition through various disease states and to quantify progression rates while considering the concurrent complication burden (15,16), that is, the complication burden at a given time point in the observation window.

Strong evidence indicates that some risk factors play a role in all types of microvascular complications. For example, the effects of the duration of diabetes and poor glycemic control are well documented (17–20). For other risk factors, such as hypertension, an association has been established mainly for retinopathy and diabetic kidney disease (21,22). Adverse cholesterol levels and previous cardiovascular disease (CVD) are indisputably associated with a higher risk of macrovascular complications (23) and may play a role in the development of microvascular complications (24).

In a cross-sectional study, we found strong clustering among all three microvascular complications (i.e., diabetic kidney disease, retinopathy, neuropathy), suggesting that the coexistence of microvascular complications is more frequent than expected (8). However, we do not know whether the risk of developing microvascular complications depends on the individual's total complication burden. Likewise, we do not know whether the association between concurrent levels of well-characterized risk factors and microvascular complications is influenced by the existing complication burden in a person with type 1 diabetes. Multistate models can be used to assess the effect of individual risk factors and to evaluate effect modification by current complication burden on the association between concurrent risk factor level (i.e., the risk factor level at each time point in the observation window) and development of microvascular complications (15).

The complex interplay between microvascular complications and risk factors has been explored only to a limited extent. In this study, we developed a multistate model of microvascular complications to describe in detail complication development in type 1 diabetes. We describe the development of sequences of diabetes-related microvascular complications at various states and examine the associations between selected risk factors, both alone and combined with existing complication burden, and incidence of (further) microvascular complications.

RESEARCH DESIGN AND METHODS

Data Sources and Study Population

In this observational cohort study, we used a clinical cohort of individuals with type 1 diabetes registered at the Steno Diabetes Center Copenhagen (SDCC), a specialized hospital for diabetes care in Denmark. We examined the development of three microvascular complications in the period of 2001–2013: diabetic kidney disease, retinopathy, and neuropathy.

Type 1 diabetes was defined in accordance with the epidemiological definition used in the Danish National Diabetes Quality Database: glucose management with insulin treatment and diagnosis at $\leq$30 years of age or an absolute need for insulin in glucose management in combination with low C-peptide values and/or GAD-65 antibody positivity in persons $>$30 years of age at diagnosis. To be included in the study, individuals were to have had a valid assessment of all three microvascular complications. Individuals with three complications at first assessment were not included in the study. Baseline was set at the date of first registration with full data available on measures of diabetic neuropathy, diabetic retinopathy, and diabetic kidney disease at least 6 months after the diagnosis of diabetes to exclude extreme metabolic values. All individuals were followed until death, incidence of all three microvascular complications, date of exit from SDCC care, or end of study (30 September 2013).

The data set included information on date of birth, debut of diabetes, date of entry and exit from SDCC, and dates of examination for microvascular complications. Variables obtained from the electronic patient record were BMI, estimated glomerular filtration rate (eGFR), systolic and diastolic blood pressure, and biochemistry laboratory information on HbA_{1c}, serum creatinine, HDL and LDL cholesterol, total cholesterol, and triglycerides. Included variables were assessed every 3–4 months. However, if data were not collected, we used last information carried forward. We also had updated information on the use of antihypertensive and lipid-lowering medications and daily insulin dose (units per kilogram of body weight). Information on the date of diagnosis of macrovascular disease (CVD, including ischemic heart disease, stroke, heart failure, or peripheral arterial disease) was extracted from the Danish National Patient Register (25). Only baseline values for smoking status, alcohol intake, physical activity, and sex were included.

Retinal images of dilated pupils were obtained with a Nikon D300S TRC-NW8 camera. Trained nurses or, if necessary, medical specialists graded the images using the Early Treatment Diabetic Retinopathy Study scale. Diabetic retinopathy or maculopathy was defined as moderate changes in either eye (grade $\geq$2).

Biothesiometry measurements with bilateral testing on the big toes were used to check for peripheral neurological complications. Vibration perception testing from 0 to 50 V was performed, and an abnormal reading (on both sides) above published age-specific thresholds (26) was used to classify identified peripheral neuropathy.

For assessment of diabetic kidney disease, we used the urinary albumin-to-creatinine ratio or albumin excretion over 24 h of urine collection. Urine albumin was measured from a 24-h urine collection by immunoassay or spot urine using the Hitachi 912 Chemistry Analyzer (Roche Diagnostics, Mannheim, Germany) or VITROS 5600 Integrated System (Ortho Clinical Diagnostics, Illkirch-Graffenstaden, France). Diabetic kidney

disease was defined as albumin excretion >30 μg/mg creatinine or an excretion rate >30 mg/24 h on two different occasions within 12 months.

Statistical Analysis

We used a multistate model as shown in Fig. 1; we did not distinguish states by order of complication occurrence. We modeled state transitions using Poisson regression for time split data. Follow-up time was subdivided according to concurrent complication state; further time splits were applied at each clinical examination and at each 6-month interval. This setup enables an individual to contribute observation time in several complication categories at different times during follow-up. We examined the incidence rate (IR) for each microvascular outcome (shown by different colors in Fig.1) in individuals with various complication burdens and compared these with the IRs in individuals without any complications. Separate models were fitted for the occurrence of each of the three types of complications; thus, all four transitions marked with the same color in Fig. 1 are modeled together.

The models included diabetes duration; calendar time and age as timescales; and sex, HbA_{1c}, lipid-lowering and antihypertensive treatment, systolic blood pressure, BMI, eGFR, CVD, LDL cholesterol, insulin (units/kg/day), and smoking status as covariates. We evaluated risk factors from various domains, and the selection of risk factors and adjustment was made a priori on the basis of existing literature. In each model, we tested whether sex modified the associations between complication state and outcome. We also tested interactions between antihypertensive medication and systolic blood pressure and between lipid-lowering medication and LDL cholesterol for all outcomes. We used the same data structure for all three microvascular outcomes and parallel analysis to generate results for Fig. 2 and Tables 2 and 3.

The linearity of the effect of quantitative risk factors on outcomes was visually assessed after fitting cubic splines with three knots for the effect. All the associations could be reasonably described by a simple linear term.

First, we assessed the overall effects of baseline and concurrent value (i.e., from the most-recent clinical visit) of HbA_{1c}, CVD status, systolic blood pressure, LDL cholesterol, duration of diabetes, eGFR, BMI, and sex on the transition rates in a model also adjusted for age, lipid-lowering and antihypertensive treatment, daily insulin dose, and smoking status. From the same model, we estimated to what extent complication burden modified the effect of each selected risk factor. To test these modifications, we added an interaction term, one at a time, between the risk factor and current complication state. We used the likelihood ratio test to compare models with and without a multiplicative interaction term between the risk factor and the current complication state.

The individual status of microvascular complications was only recorded at clinical visits. Therefore, the exact date of an event is unknown (interval censoring). Some individuals were already diagnosed with one or two complications at study entry. These individuals entered the study in the achieved complication state. For individuals in whom complications developed during follow-up, a random date between the last day without and the first day with a complication was imputed using a uniform distribution because these intervals were short (months). We performed all analyses in 60 imputed data sets and combined estimates using Rubin's rules (27). We performed two sensitivity analyses: one with a strict definition of diabetic kidney disease (i.e., macroalbuminuria) and one with retinopathy defined as severe nonproliferative or proliferative retinopathy.

All estimates are reported with 95% CIs. Calculations and graphs were made in R version 3.3.3 software (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org) using the Epi package for definition and handling of multistate follow-up (16,28), the mitools package for combining estimates averaged across imputed data sets, and the mitml package for comparing models.

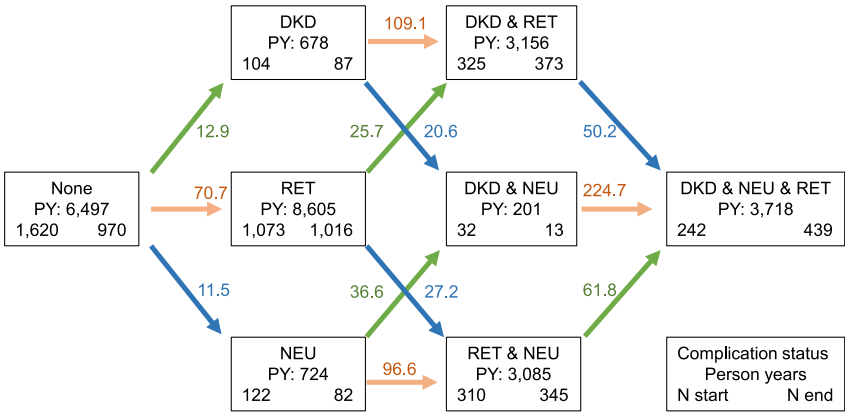

Figure 1—Patient flow in the study. Numbers are combined from 60 imputed data sets. The same individual can contribute risk time in several states during follow-up according to his or her history of complications. The numbers on the arrows are overall IR per 1,000 PY of follow-up. The numbers in the boxes are as follows: number of individuals starting in the state (bottom left), PY (middle), and number of individuals ending their follow-up in that state (bottom right). The main analysis in the study compares incidence of complications from complication states with individuals without complications separately for each complication. Thus, for each color, the three rightmost transitions are compared with the leftmost originating from the "None" state. DKD, diabetic kidney disease (green arrows); NEU, neuropathy (blue arrows); RET, retinopathy (orange arrows).

RESULTS

In total, 5,031 individuals with type 1 diabetes were registered at the SDCC during the study period. We excluded 1,203 because of missing data for diabetic kidney disease, retinopathy, and/or neuropathy, which left 3,828 eligible individuals to be included in the study. Of these, 242 were first seen in the final state with three complications, which left 3,586 available for analysis, corresponding to 22,946 person-years (PY) (Supplementary Fig. 1).

The characteristics of the included individuals at first and last clinical visit are presented in Table 1. The median follow-up time was 7.8 years (25th–75th percentile 3.3–10.7 years). HbA_{1c} level at the end of follow-up was lower than at

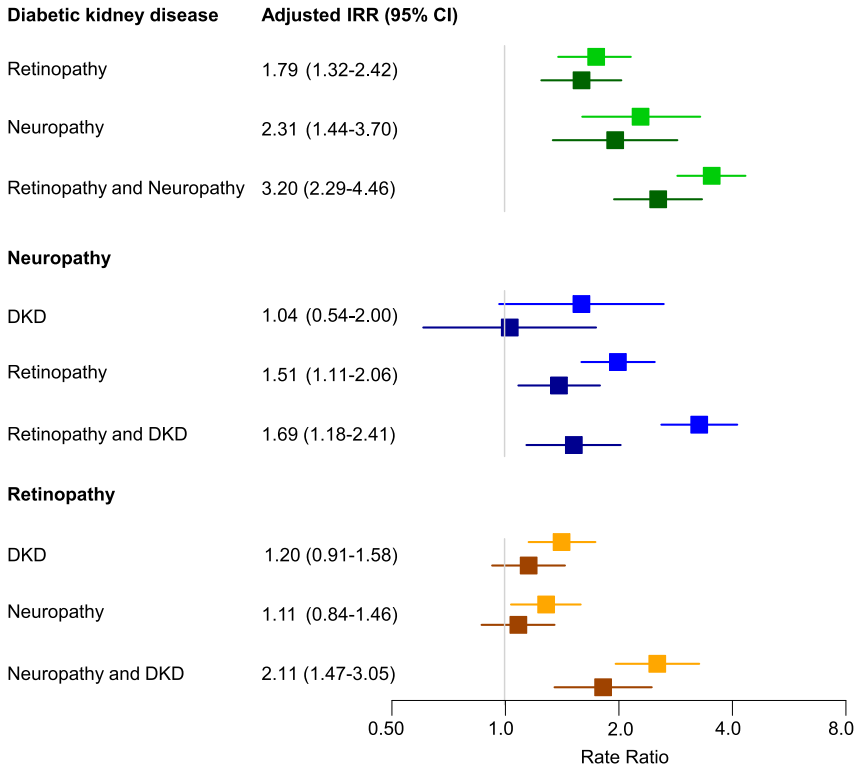

Figure 2—IRR of diabetic kidney disease (DKD), neuropathy, and retinopathy compared with individuals without complications. The estimates are derived from three transition models with different outcomes. For DKD (green), neuropathy (blue), and retinopathy (orange), colors correspond to the color of the transitions in Fig. 1. Light color indicates unadjusted estimates, and dark color indicates adjusted for sex, age (spline function), diabetes duration (spline function), HbA_{1c}, systolic blood pressure, eGFR, CVD history, insulin use (units/kg/day), BMI, antihypertensive treatment, LDL cholesterol, lipid-lowering treatment, and baseline smoking status.

entry, whereas the levels of blood pressure, lipids, and BMI were unchanged. An increase in the use of all cardioprotective medications was observed. Excluded individuals were younger at first assessment in the observation window (40 vs. 43 years; $P < 0.001$) and younger at diagnosis (18 vs. 23 years; $P < 0.001$), whereas duration of diabetes was longer (18 vs. 16 years; $P < 0.001$) than for included individuals. The proportion of men was higher among excluded individuals than among those included in the study (59% vs. 53%; $P < 0.001$). Likewise, the HbA_{1c} level at referral was higher in the excluded than in the included individuals (8.7% vs. 8.4% [72 vs. 68 mmol/mol]; $P < 0.001$). An overview of the individuals' flow between complication states in the study period is shown in Fig. 1.

Diabetic Kidney Disease

We identified 523 individuals who developed diabetic kidney disease during the study. Of these, 84 events occurred in individuals with no complications (IR 12.9 per 1,000 PY), 221 in individuals with retinopathy (25.7 per 1,000 PY), 27 in individuals with neuropathy (36.6 per 1,000 PY), and 191 in individuals with both neuropathy and retinopathy (61.8 per 1,000 PY). Figure 2 shows the IR ratio (IRR) for diabetic kidney disease in individuals at various complication states compared with individuals without microvascular complications. In the adjusted model, individuals with both retinopathy and neuropathy had a threefold higher risk of diabetic kidney disease than individuals without complications.

Neuropathy

A total of 482 individuals developed neuropathy during follow-up. Of these, 75 incidents occurred in individuals with no complications (IR 11.5 per 1,000 PY), 14 in individuals with diabetic kidney disease (20.6 per 1,000 PY), 234 in individuals with retinopathy (27.2 per 1,000 PY), and 159 in individuals with both retinopathy and diabetic kidney disease (50.2 per 1,000 PY). Individuals with both retinopathy and diabetic kidney disease had a 70% higher risk of developing neuropathy than individuals without complications (Fig. 2).

Retinopathy

In total, we recorded 649 individuals with incident retinopathy from any previous complication state. Of these, 459 incidents occurred in individuals with no complications (IR 70.7 per 1,000 PY), 74 in individuals with diabetic kidney disease (109.1 per 1,000 PY), 71 in individuals with neuropathy (96.6 per 1,000 PY), and 45 in individuals with both neuropathy and diabetic kidney disease (224.7 per 1,000 PY). Individuals with both diabetic kidney disease and neuropathy had a twofold higher IRR of developing retinopathy than individuals without complications (Fig. 2).

Effects of Individual Risk Factors

Table 2 presents the linear relationship between various risk factors at baseline and at the most-recent clinical visit and the risk of developing diabetic kidney disease, retinopathy, and neuropathy.

Diabetic Kidney Disease

Baseline and concurrent values of HbA_{1c}, systolic blood pressure, eGFR, and baseline CVD status were all strongly associated with a higher risk of developing diabetic kidney disease. The association between concurrent values of HbA_{1c} and blood pressure with diabetic kidney disease was stronger than with corresponding baseline values. The association between concurrent CVD status and incident diabetic kidney disease was modified by the individual's concurrent complication burden. The analysis that included complication state revealed that individuals without any other complications than CVD had an almost three times higher risk of diabetic kidney disease than individuals without either CVD or microvascular complications. Table 3 presents the IRRs for microvascular complications related to risk factors in individuals with various degrees of complication burden.

Retinopathy

Duration of diabetes, baseline and concurrent value of HbA_{1c}, systolic blood pressure, and baseline LDL cholesterol

Table 1—Fixed and time-dependent characteristics at entry and exit from the study

Variable	Inclusion in the study	Exit from the study*
n	3,586	3,586
Male sex	1,895 (53)	—
HbA_{1c} (mmol/mol)	66 (57–76)	62 (54–72)
HbA_{1c} (%)	8.2 (7.4–9.1)	7.8 (7.1–8.7)
Age (years)	45 (33–57)	53 (39–65)
Age at diagnosis (years)	23 (13–35)	—
Duration of diabetes (years)	18 (8–29)	25 (14–37)
Follow-up time (years)	—	7.8 (3.3–10.7)
Total cholesterol (mmol/L)	4.8 (4.2–5.4)	4.7 (4.1–5.3)
LDL cholesterol (mmol/L)	2.6 (2.1–3.2)	2.4 (2.0–3.0)
HDL cholesterol (mmol/L)	1.6 (1.3–2.0)	1.6 (1.3–2.0)
Triglycerides (mmol/L)	1.0 (0.7–1.4)	1.0 (0.8–1.4)
eGFR (mL/min/1.73 m^2)	97 (83–110)	96 (80–109)
Systolic blood pressure (mmHg)	131 (120–144)	129 (120–140)
Diastolic blood pressure (mmHg)	78 (71–84)	76 (70–82)
BMI (kg/m^2)	24.4 (22.4–26.7)	24.6 (22.3–27.3)
ACE	803 (22.4)	985 (27.5)
ARB	273 (7.6)	568 (15.8)
β-Blockers	120 (3.3)	353 (9.8)
Calcium channel blockers	331 (9.2)	704 (19.6)
Antidiuretics	638 (17.8)	930 (25.9)
Lipid-lowering treatment	581 (16.2)	1,541 (43)
Insulin dose (units/kg/day)	0.6 (0.5–0.7)	0.6 (0.5–0.8)
Insulin pump user	158 (4.4)	541 (15.1)
CVD	438 (12.2)	904 (25.2)
Smoking status (previous or concurrent)	2,252 (63.2)	—
Regular exercise	2,414 (67.9)	—
Alcohol intake >20 units/week	266 (7.5)	—
Immigrants	222 (6.2)	—

Data are median (25th–75th percentile) or *n* (%). ARB, angiotensin receptor blocker. *Last clinical assessment.

values were all factors associated with a higher risk of developing retinopathy. None of the effects of the modifiable risk factors on retinopathy were modified by complication burden. Overall, sex was not associated with the development of retinopathy. However, men with diabetic kidney disease had a higher risk of developing retinopathy than women with diabetic kidney disease.

Neuropathy

All investigated risk factors, except LDL cholesterol, were associated with incidence of neuropathy at both baseline and concurrent levels. Baseline CVD status was more strongly associated with neuropathy than concurrent CVD status, whereas associations between concurrent and baseline values and incidence of neuropathy were similar for the other risk factors. Concurrent complication burden did not modify the effect of any of the studied risk factors on the incidence of neuropathy.

Sensitivity Analyses

We performed two sensitivity analyses. The sensitivity analysis of diabetic kidney disease defined as macroalbuminuria showed that the proportion of individuals with prevalent diabetic kidney disease at inclusion was strongly reduced and that the incidence of diabetic kidney disease was much lower than in our main analysis. The adjusted IRR estimates were robust to the new definition, but the CIs were much wider because of the very low number of individuals with more complications (data not shown).

In addition, we conducted a sensitivity analysis with retinopathy defined as severe nonproliferative or proliferative retinopathy. The prevalence and incidence of retinopathy were much lower, but all associations were similar to the main analysis (data not shown). We found no effect modification by lipid-lowering or antihypertensive treatment.

CONCLUSIONS

In this study, our aim was to explore the combined effect of complication burden and the concurrent risk factor level on the risk of developing further microvascular complications. We followed 3,586 individuals with type 1 diabetes for the development of three microvascular complications and show that individuals with any previous microvascular complication had a higher risk of developing further microvascular complications than individuals without any complications. We found a stepwise higher risk of any microvascular complication in individuals with higher concurrent complication burden. Baseline and concurrent HbA_{1c} levels, systolic blood pressure, and duration of diabetes were associated with the development of all three microvascular complications. For most risk factors, we did not find evidence that concurrent complication burden modified the association with complication development.

Large randomized controlled trials have established that the main drivers of the development of microvascular complications are HbA_{1c} and duration of diabetes (17,20,29), but metabolic risk factors, other vascular complications, and various metabolic pathways also may play a role (30–32). A direct comparison of the current results with previous literature is difficult because of the novelty of our study that used multistate analysis for modeling complication-state transitions. Other studies have reported an association between diabetic kidney disease and incidence of both retinopathy (9,10) and neuropathy (33) and an association between neuropathy and the incidence of retinopathy (34). We found no clear association among these complications separately, which could be explained by the total follow-up time in the group of individuals with only diabetic kidney disease or neuropathy; these were quite low in our study sample and may have resulted in less power in these groups.

Retinopathy was the most common complication, and a sizeable proportion of individuals had retinopathy at the start of the study. Because the prevalence and

Table 2—Association of baseline and most-recent (time-updated) covariate in relation to diabetic kidney disease, retinopathy, and neuropathy

	Diabetic kidney disease	Retinopathy	Neuropathy
HbA_{1c} baseline (per 10 mmol/mol)	1.20 (1.12–1.29)	1.23 (1.15–1.30)	1.35 (1.25–1.45)
HbA_{1c} time updated (per 10 mmol/mol)	1.25 (1.16–1.34)	1.19 (1.11–1.27)	1.37 (1.27–1.47)
CVD baseline (yes vs. no)	1.28 (1.00–1.64)	1.02 (0.75–1.38)	1.64 (1.28–2.12)
CVD time updated (yes vs. no)	1.12* (0.89–1.41)	0.97 (0.75–1.26)	1.34 (1.06–1.69)
Systolic blood pressure baseline (per 10 mmHg)	1.06 (1.01–1.12)	1.08 (1.03–1.15)	1.05 (0.99–1.11)
Systolic blood pressure time updated (per 10 mmHg)	1.17 (1.11–1.23)	1.08 (1.02–1.15)	1.06 (1.00–1.13)
LDL cholesterol baseline (per mmol/L)	1.07 (0.95–1.22)	1.14 (1.01–1.28)	1.10 (0.97–1.25)
LDL cholesterol time updated (per mmol/L)	1.04 (0.92–1.17)	1.06 (0.94–1.21)	0.98 (0.86–1.12)
Duration of diabetes time updated (per 10 years)	1.05 (0.97–1.14)	1.25 (1.17–1.33)	1.19 (1.10–1.29)
Sex (male vs. female)	1.14 (0.94–1.38)	0.96* (0.81–1.14)	2.49 (2.04–3.05)
BMI baseline (per kg/m^2)	0.98 (0.95–1.01)	1.01 (0.98–1.03)	1.03 (1.00–1.06)
BMI time updated (per kg/m^2)	0.97 (0.95–1.00)	1.01 (0.99–1.04)	1.04 (1.02–1.07)
eGFR baseline (per 10 mL/min/1.73 m^2)	0.85 (0.80–0.91)	0.95 (0.89–1.01)	0.90 (0.84–0.95)
eGFR time updated (per 10 mL/min/1.73 m^2)	0.84 (0.80–0.89)	0.96 (0.90–1.02)	0.91 (0.86–0.96)

Data are IRR (95% CI). All models were adjusted for sex, age (spline function), diabetes duration (spline function), HbA_{1c}, systolic blood pressure, eGFR, BMI, lipid-lowering and antihypertensive treatment, CVD history, insulin use (units/kg/day), and smoking status. Estimates from 60 imputed data sets were combined with Rubin's rules. *Indicates that association between risk factors and events is modified by concurrent complication burden.

incidence of microvascular complications in the current study highly depended on the definition of microvascular complications, two sensitivity analyses were carried out. All associations were stable in these analyses, which used a more strict definition of diabetic kidney disease and retinopathy compared with our main results. Prevalence and IRs were lower, as expected. The incidence of complications also depended on the timing of the screening for complications. The interval between urine measures usually is 3–4 months, whereas the interval between neuropathy and retinopathy screenings can be up to 2 years. This means that individuals may have developed retinopathy or neuropathy before diabetic kidney disease, but diabetic kidney disease might be diagnosed first as a result of the timing of the screenings. We were not able to test whether the differences in screening intervals affected our results.

Concurrent risk factor levels are of higher interest than baseline levels because the latter represent a random time point in a patient's disease course. A stronger association has been shown between incidence of CVD and concurrent levels of risk factors rather than baseline level (23). The same applies for the association between HbA_{1c} and microvascular complications (29), and this pattern may be similar between other risk factors and incidence of microvascular complications. In addition, the effect of risk factors may be modified by the concurrent complication status.

The use of concurrent values allowed us to explore the impact of the investigated risk factors closer to the time of the development of complications, and this could represent values that are more relevant. Concurrent HbA_{1c} level was a strong risk factor for all microvascular complications, even when we adjusted for age, duration, and other traditional risk factors. The overall effects were of similar magnitude to the effect of baseline levels of HbA_{1c} and to other reports (11,29). In addition, concurrent diabetes duration and systolic blood pressure were associated with a higher risk of microvascular complications, whereas concurrent eGFR and CVD status were associated with diabetic kidney disease and neuropathy. Of note, baseline CVD status showed a stronger association with diabetic kidney disease and neuropathy than concurrent status. This might be explained by a lag period for the effect of CVD. If the risk of developing complications after CVD does not rise immediately, there will be a lag period before the incidence of microvascular complications increases. This implies that baseline CVD status appears to have a stronger association than concurrent CVD status.

Strengths and Limitations

The use of a long-standing electronic database of clinically collected data in a well-structured standardized setting over one decade is unique and a major strength of our register-based study. Multistate models offer the opportunity to give a detailed description of several states that individuals usually go through during a life course with type 1 diabetes. Our study is unique because we followed the individuals through various disease states while accounting for concurrent complication burden, which allowed us to study the effect of concurrent risk factor levels. The results are likely to resemble the clinical case, where physicians are likely to use the most recently available clinical information and complication status when treating patients. Thus, the current findings could facilitate better integrated risk and treatment models for type 1 diabetes in the various phases.

Another strength of this study is the sizeable study population, which allowed us to evaluate and adjust for a wide range of risk factors. We decided to evaluate a representative risk factor from each domain with strong and consistent associations reported in the literature. This decision was based on concerns about overadjustment and the risk of introducing type II error. The presented results are interpreted in the frame of a multistate model design, and the use of clinical data makes the results highly relevant in similar health care settings. However, because of the observational study design, we cannot draw conclusions

Table 3—Concurrent (most-recent) value for time-dependent risk factors in relation to diabetic kidney disease, retinopathy, and neuropathy

		Concurrent complication state				
		Risk of diabetic kidney disease				
Variable	Overall IRR time updated	None	Retinopathy	Neuropathy	Neuropathy and retinopathy	Likelihood ratio test *P* value
HbA_{1c} (per 10 mmol/mol)	1.25 (1.16–1.34)	1.09 (0.91–1.29)	1.36 (1.23–1.50)	1.07 (0.77–1.48)	1.22 (1.09–1.36)	0.093
Duration (per 10 years)	1.05 (0.97–1.14)	1.10 (0.91–1.33)	1.12 (1.00–1.27)	1.17 (0.91–1.50)	0.96 (0.85–1.07)	0.168
Sex (male vs. female)	1.14 (0.94–1.38)	1.25 (0.78–2.00)	1.05 (0.79–1.40)	0.80 (0.35–1.82)	1.27 (0.93–1.73)	0.653
CVD (yes vs. no)	1.12 (0.89–1.41)	2.55 (1.42–4.58)	1.20 (0.84–1.72)	1.58 (0.64–3.92)	0.87 (0.64–1.19)	0.019
LDL cholesterol (per mmol/L)	1.04 (0.92–1.17)	1.19 (0.86–1.64)	1.13 (0.94–1.36)	0.83 (0.46–1.49)	0.94 (0.78–1.14)	0.356
Systolic blood pressure (per 10 mmHg)	1.17 (1.11–1.23)	1.28 (1.11–1.47)	1.22 (1.13–1.31)	1.19 (0.97–1.46)	1.10 (1.01–1.19)	0.194
BMI time updated (per kg/m^2)	0.97 (0.95–1.00)	0.99 (0.93–1.06)	1.00 (0.96–1.03)	1.05 (0.94–1.17)	0.94 (0.90–0.98)	0.079
eGFR (per 10 mL/min/1.73 m^2)	0.84 (0.80–0.89)	0.78 (0.69–0.89)	0.85 (0.78–0.92)	0.73 (0.61–0.87)	0.87 (0.81–0.94)	0.184
		Risk of retinopathy				
Variable	Overall IRR time updated	None	Diabetic kidney disease	Neuropathy	Diabetic kidney disease and neuropathy	Likelihood ratio test *P* value
HbA_{1c} (per 10 mmol/mol)	1.19 (1.11–1.27)	1.20 (1.11–1.27)	1.24 (1.04–1.48)	1.24 (1.00–1.53)	0.94 (0.72–1.22)	0.283
Duration (per 10 years)	1.25 (1.17–1.33)	1.27 (1.17–1.37)	1.27 (1.07–1.50)	1.24 (1.06–1.45)	1.14 (0.95–1.36)	0.740
Sex (male vs. female)	0.96 (0.81–1.14)	0.98 (0.80–1.20)	1.54 (0.93–2.56)	0.73 (0.44–1.22)	0.44 (0.22–0.86)	0.025
CVD (yes vs. no)	0.97 (0.75–1.26)	0.86 (0.60–1.23)	1.21 (0.67–2.20)	1.31 (0.71–2.40)	0.88 (0.46–1.68)	0.581
LDL cholesterol (per mmol/L)	1.06 (0.94–1.21)	1.05 (0.90–1.22)	1.07 (0.74–1.54)	0.98 (0.66–1.44)	1.26 (0.84–1.89)	0.777
Systolic blood pressure (per 10 mmHg)	1.08 (1.02–1.15)	1.10 (1.02–1.18)	1.05 (0.90–1.23)	1.06 (0.91–1.24)	1.05 (0.88–1.27)	0.910
BMI time updated (per kg/m^2)	1.01 (0.99–1.04)	1.02 (0.99–1.05)	0.98 (0.91–1.04)	1.00 (0.93–1.08)	1.00 (0.93–1.09)	0.591
eGFR (per 10 mL/min/1.73 m^2)	0.96 (0.90–1.02)	0.95 (0.88–1.03)	0.92 (0.82–1.02)	0.98 (0.85–1.14)	1.00 (0.88–1.14)	0.676
		Risk of neuropathy				
Variable	Overall IRR time updated	None	Diabetic kidney disease	Retinopathy	Diabetic kidney disease and retinopathy	Likelihood ratio test *P* value
HbA_{1c} (per 10 mmol/mol)	1.37 (1.27–1.47)	1.33 (1.12–1.59)	1.27 (0.84–1.92)	1.39 (1.24–1.56)	1.36 (1.20–1.55)	0.863
Duration (per 10 years	1.19 (1.10–1.29)	1.18 (0.99–1.41)	1.39 (0.97–2.00)	1.20 (1.08–1.35)	1.15 (1.00–1.32)	0.817
Sex (male vs. female)	2.49 (2.04–3.05)	2.47 (1.47–4.18)	3.20 (0.77–13.75)	2.95 (2.20–3.96)	1.94 (1.38–2.72)	0.306
CVD (yes vs. no)	1.34 (1.06–1.69)	1.91 (1.02–3.58)	1.84 (0.54–6.34)	1.20 (0.85–1.68)	1.34 (0.94–1.90)	0.601
LDL cholesterol (per mmol/L)	0.98 (0.86–1.12)	0.78 (0.54–1.12)	0.91 (0.37–2.26)	1.00 (0.82–1.22)	1.04 (0.86–1.27)	0.483
Systolic blood pressure (per 10 mmHg)	1.06 (1.00–1.13)	1.09 (0.92–1.28)	1.15 (0.82–1.60)	1.07 (0.98–1.17)	1.04 (0.94–1.14)	0.848
BMI time updated (per kg/m^2)	1.04 (1.02–1.07)	1.05 (0.99–1.13)	1.02 (0.86–1.21)	1.07 (1.03–1.10)	1.01 (0.96–1.05)	0.193
eGFR (per 10 mL/min/1.73 m^2)	0.91 (0.86–0.96)	0.83 (0.72–0.97)	0.85 (0.67–1.08)	0.88 (0.80–0.97)	0.94 (0.88–1.99)	0.353

Data are IRR (95% CI). Data are adjusted for all values in the table and for age, smoking status, lipid-lowering and antihypertensive treatment, and daily insulin dose (units/kg/day), and in each model, we included an interaction term between each separate variable and concurrent complication state. Likelihood ratio estimated is from the test between models, including interaction between concurrent state and variables under scope compared with models without interaction included. Rubin's rules combine estimates and *P* values from 60 imputed data sets.

about causality. The positive associations among complications might reflect that diabetic kidney disease takes the longest time to develop, whereas retinopathy and neuropathy develop faster. Associations of two disease complications to a third might not be causal. However, that the risk of a third complication, even after adjustment for multiple confounders, is higher regardless of the previous combination of complications indicates that an association cannot be explained by these risk factors alone. In addition, concurrent risk factor levels may be subject to reverse causality. The current results should be seen as a benchmark for others who aim to explore the occurrence of microvascular complications as a function of the concurrent total complication burden in individuals with type 1 diabetes.

Selection bias also might have been introduced because of our inclusion criteria, which required availability of valid assessments of all three microvascular complications. Excluded individuals were younger, but they had been diagnosed with diabetes for a longer period when they attended the SDCC, and they had higher HbA_{1c}, which implies that they would be likely to develop microvascular complications. If they had been included, we might have found higher IRs from each state. Still, the IRR from advanced states compared with individuals without complications would not be as sensitive to this selection because it compares rates.

This study is anchored in a clinical setting where risk factors are measured repeatedly. The results show similar effects of risk factors on the risk of the three microvascular complications, and we were not able to identify specific biomarkers for certain diabetic microvascular complications. Although analyses were performed in a large clinical cohort, additional studies are needed in this area to replicate our findings and extend our knowledge.

Conclusion

This study provides a novel and detailed method to quantify the association among concurrent complication burden, several risk factors, and the occurrence of further microvascular complications in type 1 diabetes. We also examined the effect-modifying role of complication burden on the association between risk factors and development of microvascular complications. The findings demonstrate that high concurrent complication burden elevates the risk of all three investigated microvascular complications: diabetic kidney disease, retinopathy, and neuropathy. This means that if an individual develops a complication, the clinician should be aware of the increased risk of developing more complications.

We investigated the impact of risk factors at the time point closest to the diagnosis of microvascular complications. These concurrent levels are likely to represent the values that clinicians routinely use to decide on the course of action. For most risk factors, including HbA_{1c}, we found no evidence that the effect on the development of microvascular complications was modified by the burden of concurrent complications.

The results emphasize the importance of regular assessment of microvascular complications when evaluating the risk of future microvascular complications. Furthermore, the findings suggest that adequate risk factor control is equally important, regardless of the current number of complications, to prevent the development of further microvascular complications.

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Author Contributions. L.B. designed the study, analyzed the data, and wrote the manuscript. A.H. and B.C. analyzed the data and reviewed and edited the manuscript. M.C. designed the study and reviewed and edited the manuscript. M.E.J. and D.R.W. designed the study, analyzed the data, and reviewed and edited the manuscript. L.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Data Availability. The data sets generated and analyzed during this study are not publicly available because of data protection and privacy regulations. Data are available from the senior author (M.E.J.) on reasonable request.
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