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# Analysis of the duration and extent of the legacy effect in patients with type 2 diabetes: A real-world longitudinal study

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ABSTRACT

*Aims:* To analyze the duration and extent of the legacy effect on diabetic complications in real-world patients with type 2 diabetes.
*Methods:* This was a retrospective cohort study. We included the following three cohorts of patients: diabetic retinopathy (DR) (n = 1107), diabetic kidney disease (DKD) (n = 1486), and cardiovascular disease (CVD) (n = 1485). Patients were enrolled from 1995 to 1999 and followed up to 2017. Endpoints were DR incidence, ≥40% decrease in estimated glomerular filtration rate, and CVD incidence. The relationships between HbA1c as a time-dependent variable and the risk of reaching each endpoint were analyzed using multivariate Cox regression models.
*Results:* A total of 313 patients developed DR, 316 developed DKD, and 177 developed CVD. Hazard ratios as a function of time-dependent HbA1c (moving mean) accumulated over time. This accumulation was largest for DR, followed by DKD and CVD. The hazard ratios for each endpoint reached a plateau during the preceding 14–19 years.
*Conclusions:* The effect of past glycemic control may continue during 14–19 years, with a greater effect during ≤10 years. Therefore, the end of the legacy effect could be 15–20 years. This effect may be the greatest for DR, followed by DKD, and the smallest for CVD.



## 1. Introduction

The effects of early glycemic control continue over a decade, despite subsequent equivalency of glycemia in patients with type 1 and type 2 diabetes, and this is called "metabolic memory" or the "legacy effect".[1–5] However, recent studies have suggested that the benefits of early glycemic control decrease over time, although they still significantly persist, which is evident across microvascular complications.[6–9] This decline is considered to be partly due to waning of metabolic memory over time.[9] Moreover, a beneficial metabolic memory on the underlying incidence of any cardiovascular disease (CVD) may diminish with a longer follow-up.[10] However, relevant studies on this issue in the real-world condition are scarce. Furthermore, the duration and extent of the metabolic memory or legacy effect are unclear.

The mechanisms responsible for the legacy effect are recognized as involving oxidative stress, advanced glycation end-products, and epigenetic mechanisms accounting for self-perpetuating modifications of gene expression.[11] Most recently, a retrospective cohort study with an average follow-up time of 13 years showed that the legacy effect exists outside of clinical trials, begins as early as the first year after diagnosis, and depends on HbA1c levels.[12] Furthermore, the absence of a threshold in HbA1c levels for development of diabetic complications has been reported.[13]

Therefore, we analyzed the relationships between various time periods of exposure to HbA1c levels and the risk of developing microvascular and macrovascular complications using a database of real-world observations with long-term follow-up in patients with type 2 diabetes. We aimed to estimate the duration and extent of the legacy effect in a real-world setting.

## 2. Subjects, materials and methods

### 2.1. Study participants

This was a retrospective, observational cohort study. Of the 5510 people who first visited the outpatient clinic of our hospital between January 1995 and December 1999, 1547 were diagnosed with type 2 diabetes and followed-up for ≥1 year, including at least once annually. Of these 1547 patients, 1107 had no diabetic retinopathy (DR) at baseline

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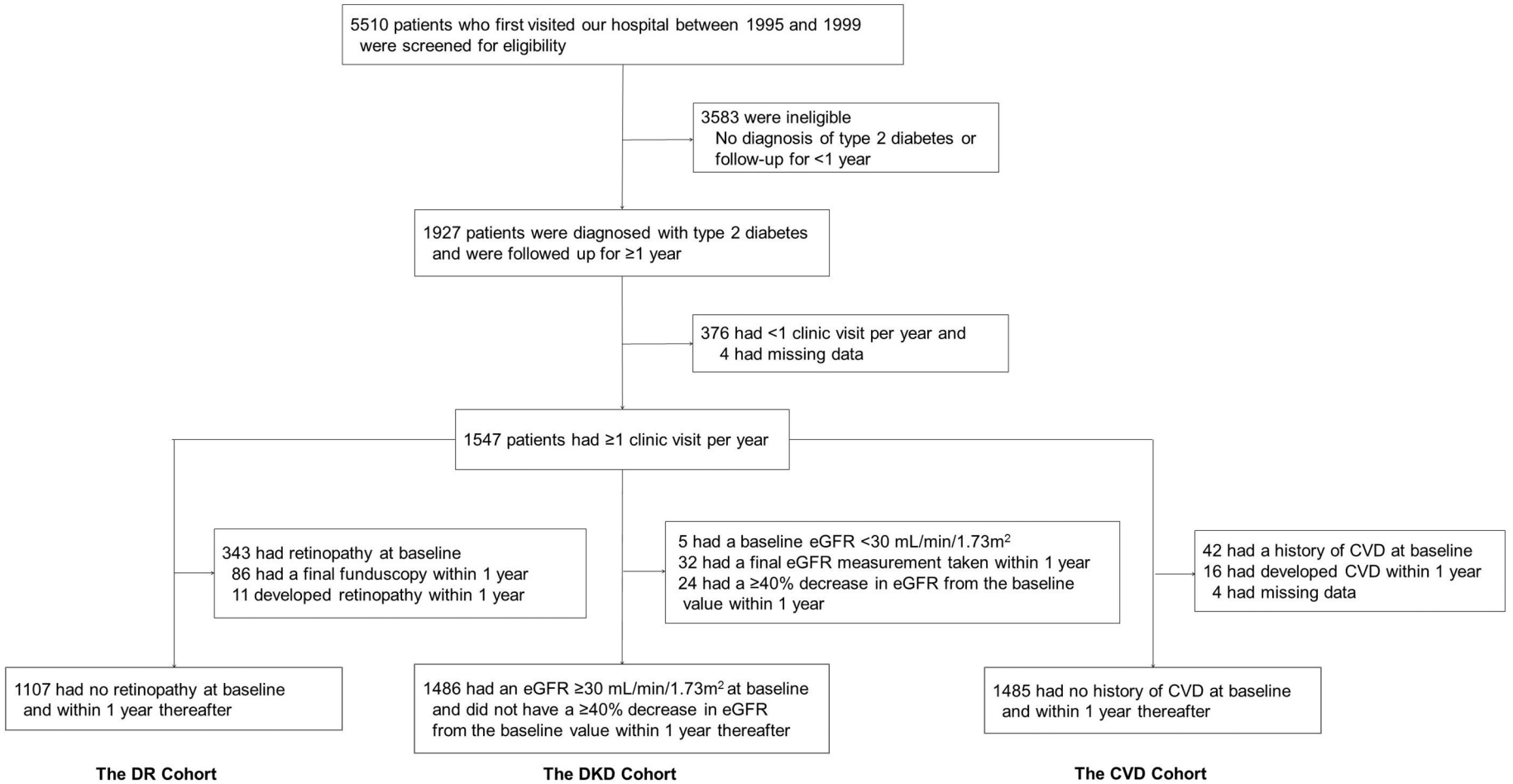



**Fig. 1.** Kaplan-Meier Estimates of the development of mild-to-moderate NPDR Flowchart for recruitment of the diabetic retinopathy (DR) cohort, the diabetic kidney disease (DKD) cohort, and the cardiovascular disease (CVD) cohort. eGFR, estimated glomerular filtration rate.

and within 1 year thereafter. Furthermore, 1486 patients had an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.72 $m^2$ at baseline and did not have a ≥40% decrease in eGFR from the baseline value within 1 year thereafter. Finally, 1485 patients had no history of CVD at baseline and within 1 year thereafter. The 1107 patients were designated as the DR cohort, the 1486 patients as the diabetic kidney disease (DKD) cohort, and the 1485 patients as the CVD cohort. We excluded the following patients from the DR cohort: patients who had DR at baseline, those who underwent a final funduscopic examination within 1 year from the first visit, and those who developed DR within 1 year from the first visit. We excluded the following patients from the DKD cohort: patients who had an eGFR <30 mL/min/1.72 $m^2$ at baseline, those who had a final eGFR measurement within 1 year from the first visit, and those who had an decreased eGFR by at least 40% of the baseline value within 1 year from the first visit. We excluded the following patients from the CVD cohort: patients who had a history of CVD at the first visit, those who developed CVD within 1 year from the first visit, and those with missing data (Fig. 1). These three cohorts were followed until 2017.

The following baseline characteristics of the three cohorts were analyzed: age, sex, duration of diabetes, blood pressure (BP), body mass index (BMI), HbA1c levels, serum lipid levels, serum creatinine (SCr) levels, estimated glomerular filtration rate (eGFR), smoking habit, alcohol intake, type of diabetes treatment, and use of antihypertensive medication and/or use of lipid-lowering drugs. Initial therapy was defined as treatment within 6 months from the first visit. Patients who received insulin alone or a combination of insulin and an oral antidiabetic agent were considered as insulin-treated.

The study design complied with the Japanese Government's Ethical Guidelines for Medical and Health Research Involving Human Subjects in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Institute for Adult Diseases, Asahi Life Foundation.

### 2.2. Clinical examinations and measurement methods

HbA1c levels were determined at each visit with an automated glycohemoglobin analyzer (Tosoh Bioscience, Tokyo, Japan) using high-performance liquid chromatography that was standardized by the Japan Diabetes Society. HbA1c values that were obtained before January 2007 were converted to Japan Diabetes Society standard values using linear regression equations, which were derived from duplicated assays using old and/or new devices or standard substances. From June 2012, we used the National Glycohemoglobin Standardization Program (NGSP)-certified method. All HbA1c (%) values before this time were converted to NGSP values[14] and International Federation of Clinical Chemistry (IFCC) values (mmol/mol).[15]

BP was typically measured twice at the first visit in the sitting position by a trained medical technologist using an electronic sphygmomanometer (OMRON, Kyoto, Japan), and the second BP value was usually recorded. Lipids were measured irrespective of fasting or postprandial status. Total cholesterol (TC) levels were determined using an enzymatic method. High-density lipoprotein cholesterol (HDLC) levels were measured using a dextran sulfate and magnesium precipitation method until April 25, 1996. HDLC levels were converted to direct enzymatic method equivalents using a linear regression equation that was derived from duplicate assays. SCr data that were obtained using the Jaffe-Rate method until June 11, 1995, were converted to the enzymatic method equivalents using a linear regression equation that was derived from duplicate assays. The eGFR was determined using the equation advocated by the Japanese Society of Nephrology.[16]

### 2.3. Definition of endpoints

Ophthalmologists who specialized in diabetes determined the presence of DR at least once a year by a mydriatic indirect funduscopic examination, a slit-lamp biomicroscopic fundus examination using a precorneal lens, and fluorescein angiography if required. The endpoint of DR was defined as development of mild-to-moderate nonproliferative DR (NPDR).[17] When a microaneurysm, dot/blot hemorrhage, or hard exudate was observed at one or more sites in at least one eye on two consecutive occasions, the first time point was defined as the time of developing mild-to-moderate NPDR. Patients who did not develop DR and did not complete the follow-up were regarded as censored cases.

The endpoint for DKD was defined as the time to a sustained decrease of at least 40% in the eGFR from baseline. Patients who did not reach the endpoint and did not complete the follow-up were considered censored cases on the final day of measuring the eGFR.

The endpoint of CVD was the first CVD event, which was defined as fatal or non-fatal acute myocardial infarction, a coronary artery procedure (bypass surgery or angioplasty), or stroke (ischemic or hemorrhagic) that required hospitalization. Patients who did not develop any CVD event and did not complete the follow-up were considered censored cases.

### 2.4. Statistical analysis

Data are expressed as mean ± standard deviation (SD) for continuous variables or as number and percentage for categorical variables. The follow-up period and the number of HbA1c measurements are described as median values (interquartile range [IQR]).

The relationships between HbA1c levels according to different time periods and the risk of each endpoint were analyzed using multivariate Cox regression models. HbA1c was analyzed as a baseline and a time-dependent covariate using the last observation carried forward (LOCF) and moving mean approaches. The 1-year period preceding each event or censoring was defined as a time window. The moving mean HbA1c values of each patient during the time windows were used in Cox regression analysis as a covariate, and the hazard ratio (HR) was calculated. The analysis was repeated 22 times by moving the time window (from 1 to 22 years preceding the event or censoring) and the HRs were plotted (Fig. 2). Covariates included age, sex, duration of diabetes, BMI, systolic BP (SBP), TC, HDLC, and smoking status at baseline.

The SAS version 9.4 software package (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Two-tailed $P$ values <0.05 were considered significant.

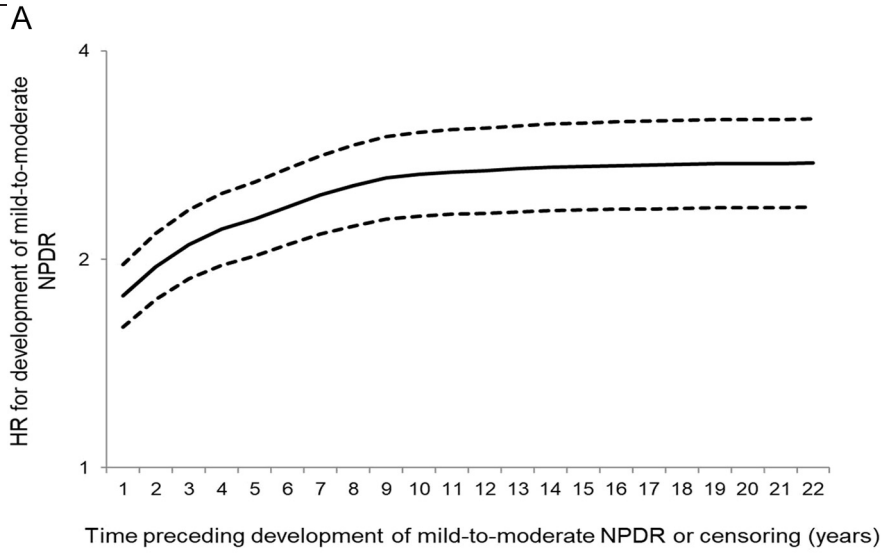
## 3. Results

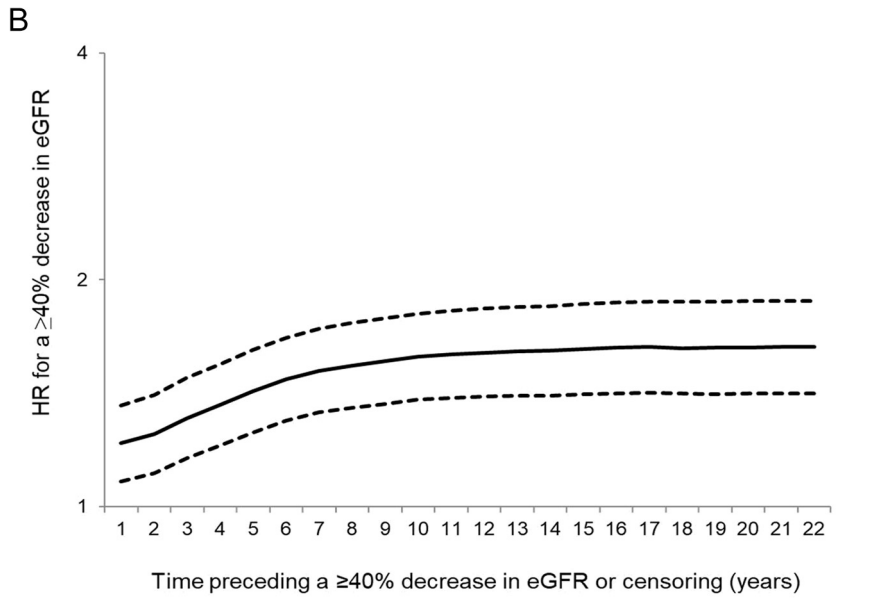
### 3.1. Baseline characteristics of the three cohorts

Table 1 shows the baseline clinical characteristics of the three cohorts. In these cohorts, the proportion of men was high and the mean (±SD) age was 56 ± 9 years. The mean duration of diabetes was 5.0 ± 5.9 years, 6.4 ± 7.2 years, and 6.2 ± 7.0 years in the DR, DKD, and CVD cohorts, respectively. The mean HbA1c level was 8.0% ± 1.7% (64[18] mmol/mol) in the DR cohort, 8.1% ± 1.7% (65[18] mmol/mol) in the DKD cohort, and 8.1% ± 1.7% (65[19] mmol/mol) in the CVD cohort. Renal function was normal in the three cohorts.

### 3.2. Endpoints occurrence, follow-up periods, and the number of HbA1c measurements

During the follow-up period, mild-to-moderate NPDR occurred in 313 (28.3%) patients (242 men, 71 women), there was a ≥ 40% decrease in eGFR in 316 (21.3%) patients (237 men, 79 women), and CVD occurred in 177 (11.9%) patients (142 men, 35 women). The median (IQR) values of the follow-up periods were 7.9 (3.9–14.8) years for the DR cohort, 9.7 (4.2–17.0) years for the DKD cohort, and 10.4 (4.6–18.5) years for the CVD cohort. Kaplan-Meier plots are shown in


A
HR for development of mild-to-moderate NPDR
4
2
1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Time preceding development of mild-to-moderate NPDR or censoring (years)


B
HR for a ≥40% decrease in eGFR
4
2
1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Time preceding a ≥40% decrease in eGFR or censoring (years)

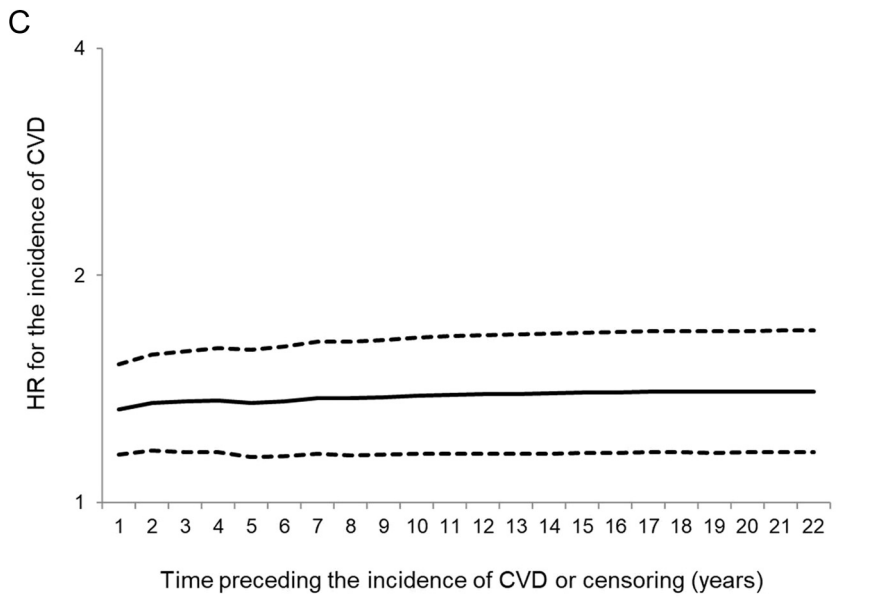

C
HR for the incidence of CVD
4
2
1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Time preceding the incidence of CVD or censoring (years)

**Table 1**
Baseline characteristics of patients in the three cohorts.

| | DR cohort | DKD cohort | CVD cohort |
|---|---|---|---|
| n | 1107 | 1486 | 1485 |
| Male (%) | 894 (80.8) | 1182 (79.5) | 1177 (79.3) |
| Age (years) | 56.2 ± 9.1 | 56.7 ± 9.4 | 56.5 ± 9.4 |
| Duration of diabetes (years) | 5.0 ± 5.9 | 6.4 ± 7.2 | 6.2 ± 7.0 |
| BMI (kg/m$^2$) | 23.2 ± 3.1 | 23.2 ± 3.2 | 23.2 ± 3.3 |
| HbA1c (%) | 8.0 ± 1.7 | 8.1 ± 1.7 | 8.1 ± 1.7 |
| (mmol/mol) | 64 ± 18 | 65 ± 18 | 65 ± 19 |
| SBP (mmHg) | 130.2 ± 19.6 | 131.9 ± 20.2 | 132.0 ± 20.5 |
| DBP (mmHg) | 76.1 ± 11.9 | 76.7 ± 19.4 | 76.4 ± 12.0 |
| TC (mmol/L) | 5.56 ± 0.99 | 5.56 ± 1.02 | 5.58 ± 1.03 |
| HDLC (mmol/L) | 1.33 ± 0.35 | 1.34 ± 0.36 | 1.35 ± 0.36 |
| eGFR (mL/min/1.73 m$^2$) | 79.6 ± 17.0 | 79.8 ± 18.6 | 80.0 ± 19.0 |
| Current smoker | 448 (40.5) | 583 (39.2) | 595 (40.1) |
| Alcohol intake | 687 (62.2) | 868 (58.7) | 874 (59.1) |
| Initial therapies | | | |
| Oral antidiabetic drugs only | 486 (43.9) | 682 (45.9) | 675 (45.5) |
| Insulin[a] | 96 (8.7) | 218 (14.7) | 214 (14.4) |
| Antihypertensive agents | 218 (19.7) | 329 (22.1) | 314 (21.1) |
| Lipid-lowering agents | 149 (13.5) | 201 (13.5) | 189 (12.7) |

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.
Values are number (%) or mean ± SD.
[a] Including patients treated with insulin alone or a combination of insulin and oral antidiabetic drugs.

Supplementary Figs. 1–3. The median (IQR) number of HbA1c measurements per patient during each follow-up period was 61 (28–110) times for the DR cohort, 74 (32−130) times for the DKD cohort, and 78 (33–139) times for the CVD cohort.

### *3.3. HbA1c as a baseline value and a time-dependent variable (LOCF), and the risk of each endpoint*

Baseline HbA1c and time-dependent HbA1c values and their relationships with the three endpoints are shown in Table 2. Multivariate Cox regression analyses showed that the baseline HbA1c level (1% increase) was a significant predictor of developing DR and DKD, but not of developing CVD. The HR as a function of the baseline HbA1c level (1% increase) was highest for developing DR, followed by DKD, and was lowest for CVD. Time-dependent HbA1c (LOCF) values were a significant predictor of developing DR, DKD, and CVD. The HR as a function of time-dependent HbA1c (LOCF) levels was highest for developing DR, followed by DKD, and then CVD.

### *3.4. HbA1c as a time-dependent variable (moving mean) and the risk of reaching each endpoint*

We analyzed the time-to-effect relationships between HbA1c as a time-dependent covariate using the moving mean method and the risks of developing DR, DKD, and CVD during 1–22 years preceding the event or censoring. All analyses were performed after adjusting for age, sex, duration of diabetes, BMI, systolic BP, TC levels, HDLC levels, and smoking status at baseline. The HRs and 95% confidence intervals (CIs) are shown in Table 2 and are plotted against the time preceding each endpoint or censoring in Fig. 2A–C. The HR for developing DR, as a function of time-dependent HbA1c levels, was lowest during the preceding 1 year. The HR rapidly increased during the preceding 1–3 years and gradually and steadily increased during the preceding 3–9 years. The HR became nearly constant during the preceding 19–22 years. The HR for developing DKD, as a function of time-dependent HbA1c levels, was lowest during the preceding 1 year. The HR increased during the preceding 1–6 years, and increased gradually and steadily during the preceding 6–10 years. The HR became nearly constant during the preceding 16–22 years. The HRs for developing DKD were lower and had a less steep slope compared with those for developing DR. Furthermore, the HR for the incidence of CVD, as a function of time-dependent HbA1c levels, was also lowest during the preceding 1 year. The HR increased slowly and steadily during the preceding 2–14 years. The HR became nearly constant during the preceding 14–22 years. The HRs for developing CVD were the lowest, except for the preceding 1–3 years, and had the most gradual slope of the three endpoints. In all three cohorts, the HRs as a function of time-dependent HbA1c levels during the relevant time periods were higher than those of baseline HbA1c levels, except for the preceding 1–2 years (moving mean) for developing DKD.

## 4. Discussion

Our study showed that previous exposure to HbA1c levels exerted a long-lasting cumulative effect on developing diabetic microvascular and macrovascular complications in patients with type 2 diabetes. The effect of past glycemic control (i.e., the legacy effect) may continue during 14–19 years, with a greater effect during ≤10 years. The end of the legacy effect could be 15–20 years. Our study also showed that the extent of the hyperglycemic effect for these complications differed. The greatest cumulative risk was observed for DR, followed by DKD, and was smallest for CVD.

A previous study investigated the effect of metabolic memory of HbA1c levels on developing DR by re-analyzing the Diabetes Control and Complications Trial data with respect to time-dependent effects.[18] This previous study showed that HbA1c values 2–3 years previously contributed the greatest risk, and values from up to 5 years earlier contributed more risk than did current values. Values from up to 8 years previously still had an important effect on current progression of DR.

**Fig. 2.** Time-to-effect relationships between HbA1c as a time-dependent covariate using the moving mean method and the risks of developing DR (A), DKD (B), and CVD (C) during 1–22 years preceding the event or censoring. HRs (solid line) and 95% CIs (dotted lines) were calculated after adjusting for age, sex, duration of diabetes, BMI, SBP, TC, HDLC, and smoking status at baseline. HRs and 95% CIs are plotted against the time preceding each endpoint or censoring. HRs are expressed per 1% increase in HbA1c levels. CI, confidence interval; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HDLC, high-density lipoprotein cholesterol; HR, hazard ratio; NPDR, non-proliferative diabetic retinopathy; SBP, systolic blood pressure; TC, total cholesterol.

**Table 2**
Multivariate Cox regression models including HbA1c values as baseline and time-dependent variables and their relationships with the risks of DR, DKD, and CVD.

| | Mild-to-moderate NPDR onset | | ≥40% decrease in eGFR | | CVD onset | |
|---|---|---|---|---|---|---|
| | Events/Patients: 313/1107 | | Events/Patients: 316/1486 | | Events/Patients: 177/1485 | |
| | HR (95%CI) | p | HR (95%CI) | p | HR (95%CI) | p |
| Model 1 | | | | | | |
| Baseline HbA1c | 1.33 (1.25–1.42) | <0.0001 | 1.29 (1.21–1.37) | <0.0001 | 1.09 (0.99–1.19) | 0.07 |
| Model 2 | | | | | | |
| Time-dependent HbA1c | | | | | | |
| LOCF | 1.60 (1.45–1.75) | <0.0001 | 1.33 (1.24–1.43) | <0.0001 | 1.32 (1.16–1.49) | <0.0001 |
| Model 3 | | | | | | |
| Time-dependent HbA1c | | | | | | |
| Moving-mean[a] | | | | | | |
| 1-year period | 1.77 (1.60–1.97) | <0.0001 | 1.21 (1.08–1.36) | 0.0011 | 1.33 (1.16–1.53) | <0.0001 |
| 2-year period | 1.95 (1.75–2.18) | <0.0001 | 1.25 (1.11–1.41) | 0.0003 | 1.36 (1.17–1.57) | <0.0001 |
| 3-year period | 2.10 (1.87–2.36) | <0.0001 | 1.31 (1.16–1.48) | <0.0001 | 1.36 (1.17–1.59) | <0.0001 |
| 4-year period | 2.21 (1.96–2.49) | <0.0001 | 1.37 (1.21–1.55) | <0.0001 | 1.37 (1.17–1.60) | 0.0001 |
| 5-year period | 2.29 (2.02–2.59) | <0.0001 | 1.42 (1.25–1.61) | <0.0001 | 1.35 (1.15–1.60) | 0.0003 |
| 6-year period | 2.38 (2.10–2.71) | <0.0001 | 1.48 (1.30–1.68) | <0.0001 | 1.36 (1.15–1.61) | 0.0003 |
| 7-year period | 2.48 (2.18–2.83) | <0.0001 | 1.52 (1.33–1.72) | <0.0001 | 1.38 (1.16–1.63) | 0.0002 |
| 8-year period | 2.56 (2.23–2.92) | <0.0001 | 1.54 (1.35–1.75) | <0.0001 | 1.37 (1.16–1.63) | 0.0003 |
| 9-year period | 2.62 (2.29–3.01) | <0.0001 | 1.56 (1.37–1.78) | <0.0001 | 1.38 (1.16–1.64) | 0.0003 |
| 10-year period | 2.66 (2.31–3.05) | <0.0001 | 1.58 (1.39–1.80) | <0.0001 | 1.38 (1.16–1.65) | 0.0003 |
| 11-year period | 2.68 (2.32–3.08) | <0.0001 | 1.59 (1.40–1.82) | <0.0001 | 1.39 (1.16–1.66) | 0.0003 |
| 12-year period | 2.69 (2.33–3.10) | <0.0001 | 1.60 (1.40–1.83) | <0.0001 | 1.39 (1.16–1.67) | 0.0003 |
| 13-year period | 2.70 (2.34–3.12) | <0.0001 | 1.61 (1.40–1.84) | <0.0001 | 1.39 (1.16–1.67) | 0.0004 |
| 14-year period | 2.72 (2.35–3.14) | <0.0001 | 1.61 (1.40–1.85) | <0.0001 | 1.40 (1.16–1.68) | 0.0004 |
| 15-year period | 2.73 (2.36–3.15) | <0.0001 | 1.62 (1.41–1.86) | <0.0001 | 1.40 (1.16–1.68) | 0.0004 |
| 16-year period | 2.73 (2.36–3.16) | <0.0001 | 1.63 (1.41–1.87) | <0.0001 | 1.40 (1.16–1.68) | 0.0004 |
| 17-year period | 2.74 (2.37–3.17) | <0.0001 | 1.63 (1.42–1.87) | <0.0001 | 1.40 (1.17–1.69) | 0.0004 |
| 18-year period | 2.74 (2.37–3.17) | <0.0001 | 1.62 (1.41–1.87) | <0.0001 | 1.40 (1.17–1.69) | 0.0003 |
| 19-year period | 2.75 (2.37–3.18) | <0.0001 | 1.63 (1.41–1.87) | <0.0001 | 1.40 (1.16–1.69) | 0.0004 |
| 20-year period | 2.75 (2.38–3.18) | <0.0001 | 1.63 (1.41–1.87) | <0.0001 | 1.40 (1.17–1.69) | 0.0004 |
| 21-year period | 2.75 (2.38–3.19) | <0.0001 | 1.63 (1.41–1.88) | <0.0001 | 1.40 (1.17–1.69) | 0.0004 |
| 22-year period | 2.75 (2.38–3.19) | <0.0001 | 1.63 (1.41–1.88) | <0.0001 | 1.40 (1.17–1.69) | 0.0003 |

All models were adjusted for age, sex, duration of diabetes, BMI, SBP, TC, HDLC, and current smoking.
HRs are shown per 1% increase in various HbA1c levels.
BMI, body mass index; CVD, cardiovascular disease; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LOCF, last observation carried forward; NPDR, non-proliferative diabetic retinopathy; SBP, systolic blood pressure; TC, total cholesterol.
[a] HRs and 95% CIs for the incidence of events as a function of time-dependent HbA1c levels were calculated using the moving mean method during 1–22 years preceding events or censoring.

The authors of this previous study also simulated the temporal relationship between HbA1c and complications of diabetes.[19] According to their study model, the time to maximal effect, which was reached after a period of increase, was followed by a period of decrease. Because we evaluated the cumulative effect of exposure to HbA1c levels during each time period, the time to the maximal effect was not precisely determined, but it would be comparable with the time when the curve showed a steep slope.

In our previous study with a mean follow-up period of 33 years, we showed a steady effect after accumulation of a hyperglycemic effect over time for developing proliferative DR (PDR).[20] The potential mechanisms for lasting cumulative effects may involve glycation of proteins,[21] which can differ in various organs. Our ultra-long-term study also showed that the effects of glycemic control during several years before developing PDR or censoring were no longer significant for progression to PDR.[20] As the duration of hyperglycemic exposure increased, there appears to be less effect of recent glycemic control on advanced microvascular complications. This issue remains to be clarified in future studies.

The strengths of this study are that we addressed a crucial topic related to managing diabetes and used a database that consisted of real-world observations with long-term follow-up. Additionally, HbA1c levels were frequently measured, which could contribute to the reliability of the data. However, this study has several limitations. First, this was a retrospective, observational cohort study. Potential information biases included changes in the sample examination methods with time. However, data generated by the different measurement methods were converted using linear regression equations that were derived from duplicate assays. Second, lipid levels were determined irrespective of fasting or postprandial status. Therefore, we could not use triglyceride levels as a covariate for analysis. Third, we did not take into account medications that were used during follow-up as a time-dependent covariate because there is confounding by indication of such medications in observational studies. Finally, we included patients from a single hospital in Japan and included more men than women. However, their clinical characteristics were similar to those of patients in another large-scale study in Japan.[22] Whether our findings can be generalized to other ethnic people is unclear. Therefore, international multicenter studies are warranted.

In conclusion, the effect of past glycemic control (i.e., the legacy effect) may continue during 14–19 years, with a greater effect during ≤10 years. The end of the legacy effect could be 15–20 years. This effect may be the greatest for DR, followed by DKD, and the smallest for CVD. Our findings suggest that sustained glycemic control over 14–19 years is required for preventing development of future complications. Furthermore, controlling glycemia in the previous 10 years is especially crucial for preventing development of microvascular complications.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.05.005.

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## Author contributions

T.T. contributed to the study concept and design, collected and recorded data, contributed to data analyses and interpretation, and wrote the manuscript. Y.M. contributed to data analyses and interpretation. M.S., H.Y., and M.K. were responsible for intellectual contributions. T.T. 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.

## Declaration of competing interest

The authors state that they have no competing interests.

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