

# **Historical HbA<sub>1c</sub> Values May Explain the Type 2 Diabetes Legacy Effect:**

**UKPDS nn <UKPDS series number to be added in proof>**

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**Running title:** Historical HbA<sub>1c</sub> Values Explain Legacy Effect

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## Abstract

**Objective** Type 2 diabetes all-cause mortality (ACM) and myocardial infarction (MI) glycaemic legacy effects have not been explained. We examined their relationships with prior individual HbA<sub>1c</sub> values and explored the potential impact of instituting earlier, compared with delayed, glucose-lowering therapy.

**Research design and methods** Twenty-year all-cause mortality (ACM) and myocardial infarction (MI) hazard functions were estimated from diagnosis of type 2 diabetes in 3,802 UK Prospective Diabetes Study participants. HbA<sub>1c</sub> values impact over time were analysed by weighting them according to their influence on downstream ACM and MI risks.

**Results** Hazard ratios for a 1 percentage unit higher HbA<sub>1c</sub> for ACM were 1.08 (95% CI 1.07-1.09), 1.18 (1.15–1.21) and 1.36 (1.30–1.42) at 5, 10 and 20 years respectively, and for MI 1.13 (1.11–1.15) at 5 years increasing to 1.31 (1.25–1.36) at 20 years.

Imposing a one percentage unit lower HbA<sub>1c</sub> from diagnosis generated an 18.8% (95% CI 21.1%–16.0%) ACM risk reduction 10-15 years later, whereas delaying this reduction until 10 years after diagnosis showed a 7-fold lower 2.7% (3.1%-2.3%) risk reduction. Corresponding MI risk reductions were 19.7% (22.4%-16.5%) when lowering HbA<sub>1c</sub> at diagnosis, and 3-fold lower 6.5% (7.4%-5.3%) when imposed 10 years later.

**Conclusions** The glycaemic legacy effects seen in type 2 diabetes are explained largely by historical HbA<sub>1c</sub> values having a greater impact than recent values on clinical outcomes. Early detection of diabetes and intensive glucose control from the time of diagnosis is essential to maximise reduction of the long-term risk of glycaemic complications.

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive glycaemic control, which achieved 0.9 % lower HbA<sub>1c</sub> levels on average compared with conventional glycaemic control, lowered the risk of microvascular complications in patients with type 2 diabetes (T2D).[1] The risks for all-cause mortality (ACM) and myocardial infarction (MI) were not reduced, although the 16% numerical MI risk reduction was borderline statistically significant (P=0.052). A subsequent patient-level meta-analysis of ACCORD, ADVANCE, UKPDS and VADT, however, confirmed a 15% MI risk reduction for a 0.88% lower HbA<sub>1c</sub>. [2]

Ten-year post-trial monitoring of surviving UKPDS participants, with virtually no glycaemic differences between those randomized previously to intensive or conventional glycaemic strategies, revealed relative risk reductions of 16% for ACM (P=0.007) and 15% for MI (P=0.01). [3] These findings, suggesting there is a “legacy” effect conferred by earlier improved glycaemic control with increasingly beneficial effects on ACM and MI risks over time, [3] has helped influence guidelines to advocate early more intensive post-diagnosis glucose-lowering therapy. Many patients, however, still do not reach their glycaemic targets. [4-6] As significant resources are required to promote early diabetes detection *e.g.*, screening large populations, and to optimize glycaemic control after diagnosis, it is essential for care-givers, patients and decision-makers to know to what extent early intensive glycaemic control can reduce the risk of long-term complications.

In this UKPDS analysis, we examine the degree to which relationships between individual historical HbA<sub>1c</sub> values over time and downstream risks of ACM and MI may explain the T2D glycaemic legacy effect.

## Research design and methods

### *Population*

The UKPDS design and results have been described previously.[1,3,7,8] Briefly, participants were stratified by ideal body weight ( $<120\%$  versus  $\geq 120\%$ ),[8] with non-overweight participants assigned randomly to an intensive (insulin or sulfonylurea) or conventional (diet) glycaemic management strategy. Overweight participants assigned to the intensive glycaemic strategy could also be allocated to metformin.[8] The aim for all participants was a fasting plasma glucose (FPG)  $<6.0$  mmol/L, with second-line glucose-lowering therapy permitted only if FPG values became  $>15$  mmol/L or unacceptable signs of hyperglycemia developed.

Following UKPDS closeout, all surviving participants entered a 10-year post-trial monitoring period and were returned to routine care with no attempt made to maintain trial-allocated treatment regimens.[3] They were seen annually at UKPDS centres for the first five years with collection of standardized data, including HbA<sub>1c</sub>. Thereafter, participants were followed remotely by means of annual participant- and GP-completed questionnaires.

In this analysis, only those assigned originally to an intensive glycaemic strategy with a sulfonylurea or insulin, or to a conventional glycaemic strategy with diet, were evaluated. HbA<sub>1c</sub> values were measured annually in the UKPDS. Participants were excluded if they had a missing baseline HbA<sub>1c</sub> value or did not have at least one follow-up HbA<sub>1c</sub> value recorded during the 2 years preceding ACM or MI. HbA<sub>1c</sub> values, measured as %, [7] have been converted to mmol/mol according to guidelines.[9]

### *Relationship of historical HbA<sub>1c</sub> values to downstream ACM and MI risks*

Time-to-event analysis of diabetes complications and HbA<sub>1c</sub> is commonly performed using baseline or updated mean HbA<sub>1c</sub> values.[10-13] However, none of these HbA<sub>1c</sub> metrics

consider how HbA<sub>1c</sub> values, measured at different historical timepoints, may vary in their individual contribution to the downstream risk of diabetes-related complications.

Accordingly, we used a model in which historical HbA<sub>1c</sub> values were weighted unequally to allow for different risk contributions at each timepoint. This was done using a multivariable regression model where optimal weights for historical HbA<sub>1c</sub> values were estimated simultaneously with the effect of the influence weighted HbA<sub>1c</sub> variable and coefficients for other covariates.[14,15] The overall temporal relationship of HbA<sub>1c</sub> with ACM and MI was investigated by estimating the degree to which the instantaneous risk (hazard) of ACM and MI at 15 and 20 years after diagnosis could be ascribed to HbA<sub>1c</sub> values measured at previous timepoints.

#### *ACM and MI hazard ratios in relation to HbA<sub>1c</sub>*

The impact of HbA<sub>1c</sub> values on diabetes-related complications has commonly been estimated by calculating hazard ratios (HRs) in relation to a one percentage unit (11 mmol/mol) difference in HbA<sub>1c</sub>. [10,13-15] We estimated ACM and MI HRs at five, 10, 15 and 20 years after diagnosis of diabetes assuming a one percentage unit (11 mmol/mol) higher HbA<sub>1c</sub> from diagnosis onwards. To further understand the impact of historical HbA<sub>1c</sub> levels on downstream ACM and MI risks (legacy effects), we also estimated ACM and MI HRs at 10-20 years after diagnosis in relation to a one percentage unit (11 mmol/mol) lower HbA<sub>1c</sub>, imposed at diagnosis of diabetes or delayed until five or 10 years later. These estimations were repeated for HbA<sub>1c</sub> decrements of 0.5% (5.5 mmol/mol) and 2.0% (22 mmol/mol).

#### *ACM and MI relative risks relating to historical HbA<sub>1c</sub> values*

To study how prior HbA<sub>1c</sub> values might influence the incidence of downstream ACM and MI over a longer time period, we estimated ACM and MI relative risks at 0-10, 10-15 and 10-20

years after diagnosis when a lower HbA<sub>1c</sub> was imposed immediately compared with delaying this until five or 10 years later.

### *Impact of UKPDS randomized glycaemic strategies*

To evaluate whether factors other than glycaemic control might explained differences in outcomes, we investigated the extent to which assignment to an intensive or conventional glycaemic control strategy, irrespective of achieved HbA<sub>1c</sub> values, impacted on the incidence of ACM and MI.

### *Statistical Analyses*

We used a multivariable Poisson regression model that included HbA<sub>1c</sub>, age, sex and diabetes duration with the total follow-up period for each patient subdivided into small intervals of 0.2 years, for each of which a constant hazard was assumed. HbA<sub>1c</sub> was included in the model as a time-dependent weighted integral of all prior HbA<sub>1c</sub> values, with values weighted unequally to allow for a potential different risk contribution at each timepoint. The influence weighted HbA<sub>1c</sub> variable was computed by first creating a continuous HbA<sub>1c</sub> curve using linear interpolation between observed HbA<sub>1c</sub> values, which was then weighted by a piecewise exponential weight function with one knot. The optimal HbA<sub>1c</sub> weight function parameters were estimated simultaneously with the coefficients of the covariates in the model using maximum likelihood estimation.

Likelihood ratio tests were used to assess the significance of individual model parameters, with corresponding confidence intervals computed by test inversion.[16]

Estimates and confidence intervals for influence weighted HbA<sub>1c</sub> HRs at various follow-up times, and for relative risks associated with imposed immediate or delayed HbA<sub>1c</sub> reductions, were computed from the corresponding regression coefficient, fixing the HbA<sub>1c</sub> weight

function parameters at their estimated values. Model fit was assessed by comparing observed and expected event numbers for various age categories and follow-up times. Additional model and statistical methodology details can be found here [14,15] and in the supplementary material (**Additional statistical analysis details**).

## Results

### *Patient characteristics*

Requisite UKPDS data were available for 3,802 participants with 775 ACM events, and for 3,219 participants with 662 MI events. Their mean (SD) age at diagnosis of diabetes was 53.3 (8.6) years and 38.8% were female. For ACM and MI analyses there were 3,321 (87%) and 3,219 (85%) participants respectively followed for more than five years. The number of participants included in the analyses with follow-up of more than 10 and 15 years for ACM were 2,742 (72%) and 1,299 (34%), respectively, and for MI 2,544 (67%) and 1,156 (30%), respectively.

### *ACM and MI hazard ratios in relation to HbA<sub>1c</sub>*

Higher HbA<sub>1c</sub> values were associated significantly with both higher ACM and MI risks (both  $p < 0.0001$ ). HRs for ACM and MI in relation to imposed 0.5% (5 mmol/mol), 1% (11 mmol/mol) and 2% (22 mmol/mol) higher HbA<sub>1c</sub> values during the first five, 10, 15 or 20 years following diagnosis of diabetes are presented in **Table 1**. Each 1% (11 mmol/mol) higher HbA<sub>1c</sub> was related to steadily higher HRs over time for ACM and MI, suggesting increasingly harmful effects of earlier hyperglycaemia. HRs for ACM *per* 1% (11 mmol/mol) higher HbA<sub>1c</sub> value were 1.08 (95% CI 1.07–1.09), 1.18 (1.15–1.21) and 1.36 (1.30–1.42) at

five, 10 and 20 years follow-up respectively, while MI HRs increased from 1.13 (1.11-1.15) at five years to 1.31 (1.25-1.36) at 20 years.

Imposing a one percentage unit (11 mmol/mol) lower HbA<sub>1c</sub> from diagnosis of diabetes significantly lowered the instantaneous risk (hazard) of ACM or MI events 15 and 20 years later, compared with reducing HbA<sub>1c</sub> by the same amount from 10 years after diagnosis (**Figure 1**). ACM HRs (95% CI) at 15 and 20 years after diagnosis when reducing HbA<sub>1c</sub> from diagnosis, compared with from 10 years after diagnosis, were respectively 0.78 (0.76–0.81) *vs.* 0.93 (0.92–0.94), and 0.73 (0.70–0.77) *vs.* 0.84 (0.82–0.87). Corresponding MI HRs were 0.79 (0.76–0.82) *vs.* 0.88 (0.87–0.90) and 0.76 (0.73–0.80) *vs.* 0.82 (0.80–0.85). HRs calculated when HbA<sub>1c</sub> lowering was delayed approached those of immediate HbA<sub>1c</sub> lowering somewhat more rapidly for MI than for ACM (**Figure 1**). Similar relationships over time were found for ACM and MI when HbA<sub>1c</sub> was lowered by 0.5 or 2 percentage units (**Supplementary Figures S2 and S3**).

*Relative risks of ACM and MI 10-20 years after diagnosis in relation to early or delayed imposed lowering of HbA<sub>1c</sub>*

To study glucose-lowering legacy effects over longer time periods, we estimated the effect of imposing immediate or delayed HbA<sub>1c</sub> reductions on ACM and MI risks between 0–10, 10–15 and 10–20 years after diagnosis. The estimated ACM relative risk reduction was 18.8% (95% CI 21.1–16.0) at 10–15 years *per* one percentage unit lower HbA<sub>1c</sub> when imposed from diagnosis, but seven-fold smaller at 2.7% (3.1–2.3) when imposed 10 years after diagnosis. The corresponding MI estimates showed a three-fold smaller relative risk reduction comparing delayed with immediate imposition of a lower HbA<sub>1c</sub> (**Table 2**). For the period 10–20 years after diagnosis, delayed compared with immediate imposition HbA<sub>1c</sub> lowering by one percentage unit (11 mmol/mol) resulted in an approximately 3-fold smaller ACM relative

risk reduction and a 2-fold smaller MI relative risk reduction (**Table 2**). Similar legacy effects for ACM and MI risks were seen with imposed 0.5% and 2.0% lower HbA<sub>1c</sub> values (**Supplementary Table S2**).

#### *Relationship of historical HbA<sub>1c</sub> values to downstream ACM and MI risks*

The overall temporal relationships of HbA<sub>1c</sub> with ACM and MI are shown in **Figure 2**.

HbA<sub>1c</sub> values measured during the first 10 years after diagnosis contributed to 69% (95% CI 60–75) of the HbA<sub>1c</sub> total effect on ACM risk 15 years after diagnosis, and 45% (33–54) at 20 years (**Figure 2**). The corresponding MI estimates were 49% (37–56) and 27% (16–35).

#### *Impact of age, sex and assigned glycaemic control strategy*

Older age and male sex were associated significantly (both  $p < 0.0001$ ) with increased ACM and MI risks (**Supplementary Table S1**). When HbA<sub>1c</sub> was included in the model, the glycaemic control strategy assignment (intensive vs. conventional) effect was attenuated, and not associated with ACM ( $p = 0.15$ ) or MI ( $p = 0.07$ ).

#### *Model checks*

Details of the final model estimated parameters, including coefficients of the HbA<sub>1c</sub> weight function, are provided in **Supplementary Table S1**. Several model checks were performed, with no lack-of-fit detected. The model predicted cumulative number of UKPDS participants experiencing an ACM or MI event was similar to that observed (**Supplementary Figure S4**). A sensitivity analysis to assess the impact of baseline HbA<sub>1c</sub>, that excluded HbA<sub>1c</sub> values and deaths during the first four years of after diagnosis, showed similar time-associations between HbA<sub>1c</sub> and ACM. Similar patterns were also seen when an interaction term for time and HbA<sub>1c</sub> was included in the model.

## Conclusion

### *Principal findings*

In this analysis of the UKPDS and its post-trial monitoring period we found that historical HbA<sub>1c</sub> values were associated with strong legacy effects for the downstream incidence of ACM and MI. Analyses exploring the impact of delaying the imposition of a 1% lower HbA<sub>1c</sub> until 10 years after diagnosis of diabetes, compared with doing this immediately, showed a 7-fold lower risk reduction for ACM at 10-15 years. At 10–20 years after diagnosis, the risk of death was reduced by 3-fold when HbA<sub>1c</sub> was lowered from diagnosis. Similar time-dependent effects were observed for MI, but HbA<sub>1c</sub> legacy effects were numerically greater for ACM than MI. The impact on ACM and MI risks of delaying imposition of improved glycaemic control following diagnosis of diabetes increased steadily with time. Thus, a one percentage unit (11 mmol/mol) higher HbA<sub>1c</sub> level was associated with an 8% greater ACM risk at 5 years, increasing to 36% at 20 years. The risks for ACM and MI were captured by HbA<sub>1c</sub>, whereas assigned glycaemic strategy group was not significant when HbA<sub>1c</sub> was included in the model. This finding strongly supports the fact that the long-term ACM and MI risk reductions seen in the UKPDS intensive glycaemic strategy group are driven by the early introduction of improved glycaemic control.[1,3] The somewhat stronger legacy-effect we see for ACM, compared with MI, reflects the increased ACM risk reduction from 6% to 13% during UKPDS post-trial monitoring, whilst the degree of MI risk reduction was essentially unchanged (16% vs. 15%).[3]

### *Other studies*

The existence of a strong legacy effect of earlier glycaemic control on cardiovascular disease

is supported by findings from studies of patients with type 1 diabetes (T1D). In the EDIC follow-up of the DCCT study, participants previously assigned to intensive glycaemic therapy had fewer CVD events, even though the glycaemic difference between the intensive and conventional groups was not maintained.[17,18] ACM and MI reductions were not seen with intensive glycaemic therapy in any of the three large-scale glucose-lowering studies carried out over 3-5 years in patients with generally long-standing T2D.[19-21] This may reflect the initially smaller risk reductions with improved HbA<sub>1c</sub>, or the late introduction of improved glycaemic control in patients with diabetes of long-duration. Minimizing hyperglycemia plays a major role in reducing the risk of diabetic complications, particularly microvascular complications,[1,3, 8] whilst other glucose-lowering drugs such as metformin, GLP-1 receptor analogues and SGLT-2 inhibitors likely also act via additional non-glucose lowering mechanisms to reduce ACM and MI risks.[8,22,23] Nonetheless, whilst the risks of myocardial infarction and death have reduced over time, these remain substantially higher for people with type 2 diabetes.[24, 25]

### *Explanations and interpretations*

The legacy effect of earlier hyperglycaemia on diabetic complications appears to explain the increasing impact of historical HbA<sub>1c</sub> values on ACM and MI risks over time. Legacy effects in T2D, and “metabolic memory” in T1D, have been the subject of much debate [3,17,26-29]. Certain pathways associated with diabetes complications may be active later but initiated from earlier increases in glucose, where reactive oxygen species have been proposed to play an essential role.[26,30] The reason for legacy-effects being somewhat greater for ACM than MI is speculative. It is possible that to some extent death may occur in a time delayed fashion from several diabetes related complications (including MI), a fact which may explain how HbA<sub>1c</sub> affects death and MI with time. Early hyperglycaemia leading to nephropathy,

initiating processes increasing future risks of ACM and MI, including hypertension, altered lipid metabolism and inflammatory processes may also be a major contributor.[31,32] In multiple studies, renal complications have been major risk factors for future cardiovascular disease and mortality. [13,31-33]

### *Implications*

Although early more intensive glycaemic control in UKPDS participants with newly-diagnosed T2D has shown ACM and MI risk reductions in the longer term, associations with individual historical HbA<sub>1c</sub> values and their long-term effects have not been studied. Here we show that imposing a lower HbA<sub>1c</sub> immediately after diagnosis of T2D is associated with several-fold greater risk reductions in ACM and MI 10-20 years later, compared with delayed HbA<sub>1c</sub> lowering. T2D is a worldwide epidemic affecting more than 463 million persons and causing a large proportion of severe renal, visual and cardiovascular disease events as well as amputations and shorter life expectancy.[34] In addition, many people have undetected diabetes.[34] Our results imply that societies should focus even more on early T2D detection and glucose optimisation. Moreover, programs in both children and adults without diabetes could prevent or delay diabetes onset and thereby minimize glycaemic exposure at an even earlier time period.

Guidelines today recommend screening high risk groups, *e.g.*, obese persons and first-degree relatives of individuals with T2D,[4,5] but few structural programs exist in many countries . If T2D remains undetected, glucose levels can increase over many years without symptoms but with elevated HbA<sub>1c</sub> values that are associated with greatly increased risk as we have shown here, *e.g.*, a 2% (22 mmol/mol) higher HbA<sub>1c</sub> increases ACM risk by 40% after 10 years and

86% after 20 years.

Another implication is that glycaemic control contributes more to risk of ACM and MI than previously thought. Our study found an ACM risk increase >30% at 20 years per unit HbA<sub>1c</sub> increase, compared with 10-20% in previous studies.[10-13] The difference is due to the increasing effects over time which likely will increase even more for many patients over a lifetime horizon. Besides the need for early detection of diabetes and glycaemic optimization, our findings support the need for strict glycaemic control when treating people with T2D in clinical practice. Effects of glucose-lowering treatments in CV outcome trials have likely underestimated effects of glycaemic control since the beneficial effects according to the current results increase over at least 15-20 years, *i.e.*, far beyond the duration of most studies which have generally been 3-5 years.[19-23,28,29] The increasing and larger risk reductions seen here over time need to be considered when making treatment decisions in clinical practice, writing guidelines and performing healthcare economic analyses.

These results are also of interest in light of the current Covid-19 epidemic.

Persons with type 2 diabetes with high mortality risk following Covid-19 infection are generally those with advanced diabetes complications (35, 36). To help minimise such risks in future viral epidemics, our findings highlight the crucial need for early implementation of intensive glycaemic control in people with newly-diagnosed type 2 diabetes to reduce end-organ damage.

### *Strengths and limitations*

Strengths of our study include the UKPDS long-term follow-up with detailed HbA<sub>1c</sub> and adjudicated complication data. Also, participants were followed from diagnosis of T2D, which is essential to capture as much information as possible on early hyperglycaemic effects. The model we used has previously shown a better fit than traditional models and variables used for describing HbA<sub>1c</sub> in relation to diabetic complications.[10,14,15] Although it shows a good fit here, we cannot exclude residual confounding due to the study's observational nature. In particular, partial confounding may exist between the studied HbA<sub>1c</sub> variable, which varies non-linearly with time since diagnosis, and non-linear effects of diabetes duration. None of the conducted sensitivity analyses, however, revealed any such patterns.

Since the current analyses focused on the relative impact of historical HbA<sub>1c</sub> values, we did not evaluate risk factors other than age, sex and treatment group. Moreover, it should be noted that healthy living habits, which may be associated with improved glycemic control and were not controlled for in the current analysis, can also influence the risk of AMI and mortality. For future estimations of the probability of ACM or MI for individuals it will be essential to include other risk factors and covariates. However, it is already known that HbA<sub>1c</sub> is an independent risk factor for MI and ACM as shown in multiple studies including the UKPDS (11-13). In the current study intraindividual HbA<sub>1c</sub> values, *i.e.*, for each participant, were evaluated to determine their relative contributions over time to MI and ACM. Whilst it would be of interest to determine and also adjust for time-dependent effects of other risk factors (smoking, weight, blood pressure, lipid profiles), they did not vary greatly over time in UKPDS, and such analyses would be complex to perform.

The use of statins and RAAS inhibitors in UKPDS were confined primarily to the post-trial monitoring period. It is possible that by reducing overall cardiovascular risk they might to some extent influence the effect ascribed to historical HbA<sub>1c</sub> values but not fundamentally change the relationship between HbA<sub>1c</sub> and complications.

In conclusion, the adverse effects of HbA<sub>1c</sub> on ACM and MI increase over time. Strong HbA<sub>1c</sub> legacy-effects exist for both these outcomes, but appear greater for ACM. Given these large legacy effects, early detection of T2D (screening) and glycaemic optimisation needs greater emphasis in guidelines, by health care providers and in clinical practice to more effectively prevent long-term complications and achieve a more normal life-expectancy for people with T2D.

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## **Data sharing statement**

Data may be accessed after a written research proposal and support from investigators and upon request and an appropriate data transfer agreement is in place.

## **Conflicts of interest**

ML has received research grants from DexCom and NovoNordisk and been a consultant for Astra Zeneca, Boehringer Ingelheim, DexCom, Eli Lilly, MSD and Novo Nordisk.

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**Table 1.** Hazard ratios for all-cause mortality and myocardial infarction *per* 0.5, 1 and 2 percentage unit (5.5, 11 and 22 mmol/mol) higher HbA<sub>1c</sub> (%) values over the first five, 10, 15 and 20 years following diagnosis of type 2 diabetes.

<b>Years after diagnosis</b>	<b>HR (95% CI) per 0.5 percentage units higher</b>	<b>HR (95% CI) per 1 percentage units higher</b>	<b>HR (95% CI) per 2 percentage units higher</b>
<b>All-cause mortality</b>			
<b>5</b>	1.04 (1.03 - 1.04)	1.08 (1.07 - 1.09)	1.16 (1.14 - 1.19)
<b>10</b>	1.09 (1.07 - 1.10)	1.18 (1.15 - 1.21)	1.40 (1.33 - 1.47)
<b>15</b>	1.13 (1.11 - 1.15)	1.28 (1.23 - 1.32)	1.64 (1.51 - 1.75)
<b>20</b>	1.17 (1.14 - 1.19)	1.36 (1.30 - 1.42)	1.86 (1.68 - 2.03)
<b>Myocardial infarction</b>			
<b>5</b>	1.06 (1.05 - 1.07)	1.13 (1.11 - 1.15)	1.28 (1.22 - 1.33)
<b>10</b>	1.10 (1.08 - 1.12)	1.22 (1.17 - 1.25)	1.48 (1.38 - 1.57)
<b>15</b>	1.13 (1.10 - 1.15)	1.27 (1.22 - 1.32)	1.62 (1.49 - 1.75)
<b>20</b>	1.14 (1.12 - 1.17)	1.31 (1.25 - 1.36)	1.71 (1.55 - 1.86)
Data is presented as HR (95% CI). All hazard ratios are statistically significant with $p < 0.0001$ . The hazard ratio per $z$ units increase in HbA <sub>1c</sub> during $t$ years after diagnosis is given by Equation 5 in the supplementary material. The model coefficients of the HbA <sub>1c</sub> weight function and covariates included in the model are presented in Supplementary Table S1. CI: confidence interval; HbA <sub>1c</sub> , Hemoglobin A1c; HR, Hazard ratio.			

**Table 2.** Estimated relative risks of all-cause mortality and myocardial infarction between 0–10, 10–15 and 10–20 years after diagnosis assuming a 1 percentage unit (11 mmol/mol) lower HbA<sub>1c</sub> from diagnosis, and when the same HbA<sub>1c</sub> lowering was imposed from 5 and from 10 years after diagnosis.

Years after diagnosis	HbA <sub>1c</sub> lowered at diagnosis	HbA <sub>1c</sub> lowered 5 years after diagnosis	HbA <sub>1c</sub> lowered 10 years after diagnosis
<b>All-cause mortality</b>			
<b>0–10</b>	0.928 (0.919 - 0.939)	0.987 (0.985 - 0.989)	1.00
<b>10–15</b>	0.812 (0.789 - 0.840)	0.885 (0.870 - 0.902)	0.973 (0.969 - 0.977)
<b>10–20</b>	0.785 (0.758 - 0.815)	0.848 (0.829 - 0.871)	0.928 (0.919 - 0.939)
<b>Myocardial infarction</b>			
<b>0–10</b>	0.893 (0.877 - 0.911)	0.968 (0.963 - 0.973)	1.00
<b>10–15</b>	0.803 (0.776 - 0.835)	0.851 (0.830 - 0.876)	0.935 (0.926 - 0.947)
<b>10–20</b>	0.788 (0.760 - 0.823)	0.826 (0.803 - 0.855)	0.893 (0.877 - 0.911)
Data is presented as RR (95% CI) <i>per</i> one percentage unit lower HbA <sub>1c</sub> . The relative risk of an event in a time interval 0–10, 10–15 or 10–20 years after diagnosis was calculated according to Equation 11 in the supplementary material. CI: confidence interval; HbA <sub>1c</sub> , Hemoglobin A1c; RR, Relative risk.			

## Figure legends

**Figure 1:** Time-dependent hazard ratios for all cause-mortality (left) and myocardial infarction (right) from 0 to 20 years after diagnosis of type 2 diabetes assuming a one percentage unit lower HbA<sub>1c</sub> from diagnosis (green dotted lines), and when the same degree of HbA<sub>1c</sub> lowering was imposed from 5 years (blue dashed lines) and from 10 years (red solid lines) after diagnosis. The shaded regions represent 95% confidence limits. Hazard ratios were calculated according to Equation 6 in the supplementary material.

**Figure 2:** Contribution of historical HbA<sub>1c</sub> values to their impact on instantaneous risk (hazard) of all-cause mortality (left) and myocardial infarction (right) at 15 years (red solid lines) and 20 years (blue dashed lines) after diagnosis. The legacy effect of historical HbA<sub>1c</sub> values on diabetes complications is more pronounced for ACM than for MI. The shaded regions represent 95% confidence limits. Details on the calculations may be found in Equation 7 in the supplementary material.

## **Supplementary Appendix**

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to:

### **Historical HbA<sub>1c</sub> Values May Explain the Type 2 Diabetes Legacy Effect**

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## Article I. Additional statistical analysis details

Statistical analyses were performed using Poisson regression with current (updated) age, current (updated) diabetes duration, sex (male = 1, female = 2) and an influence weighted HbA<sub>1c</sub> variable (%) as explanatory variables. The total follow-up period of each patient was subdivided into small intervals of 0.2 years where a Poisson model with constant hazard was assumed (or, equivalently, an exponential distribution for the survival time). The subdivision into small intervals makes the assumption of Poisson distribution well fulfilled, allows for time dependent covariates and enables flexible modelling of the impact of historical HbA<sub>1c</sub> values at various points in time.

### Model formulation

Using the Poisson model with piecewise constant hazard, the contribution to the likelihood function per interval of an individual is  $(l\lambda)^k \exp(-l\lambda)$ , where  $k = 0$  or  $1$  depending on whether an event (only the individual's first one) had occurred in the interval. The quantity  $l$  is the length of the contribution period in the interval (at most 0.2 years and shorter if there was an event or censoring within the interval), and  $\lambda$  is the hazard. In each time interval, the hazard  $\lambda(t)$  at time  $t$  was modelled as

$$\log(\lambda(t)) = \beta_1 + \beta_2 \times \text{Age}(\tau) + \beta_3 \times \text{Diabetes duration}(\tau) + \beta_4 \times \text{Sex} + \beta_5 \times \text{wHbA1c}(\tau), \quad (\text{Eq. 1})$$

where  $\text{Age}(\tau)$ ,  $\text{Diabetes duration}(\tau)$  and  $\text{wHbA1c}(\tau)$  are the age, diabetes duration and influence weighted HbA<sub>1c</sub> at time  $\tau = 0.2 \times [5t]$ , i.e. evaluated at the left endpoint of the current time interval. The influence weighted HbA<sub>1c</sub> variable was defined as an integral of historical HbA<sub>1c</sub> values

$$\int_0^t x(s)g(t-s)ds, \quad (\text{Eq. 2})$$

where  $x(s)$  is the HbA<sub>1c</sub> value at time point  $s$  (years since diagnosis) using linear interpolation between observed HbA<sub>1c</sub> values, and  $g(t)$  is a weight function. The weight function  $g(t)$  was defined as a piecewise exponential function with one knot:

$$g(t) = \begin{cases} \exp(b_1 t) & \text{if } t \leq b_2 \\ \exp(b_1 b_2 + b_3(t - b_2)) & \text{if } t > b_2 \end{cases}, \quad (\text{Eq. 3})$$

where  $b_1, b_2$  and  $b_3$  are parameters to be estimated. These parameters may be interpreted as follows:  $b_1$  describes an initial increase or decrease in the relative risk contribution over time from an HbA<sub>1c</sub> value, and  $b_3$  describes the increase or decrease of the relative risk contribution after the breakpoint  $b_2$ . The shape of the function  $g(t)$  for the outcomes considered in this study and with the parameters  $b_1, b_2$  and  $b_3$  estimated from data is presented in Figure S1.

### Time-dependent HbA<sub>1c</sub> hazard ratios and relative risks

Consider two continuous HbA<sub>1c</sub> curves  $\{x_0(s), s \in [0, T]\}$  and  $\{x_1(s), s \in [0, T]\}$  on a time interval from 0 to  $T$  years after diagnosis, where  $x_0(s)$  and  $x_1(s)$  are the HbA<sub>1c</sub> values at the time point  $s \in [0, T]$ . We describe below how hazard ratios and relative risks of the HbA<sub>1c</sub> profile  $x_1$  vs  $x_0$  may be calculated from the Poisson model with the hazard function defined by Equation 1–3.

*Hazard ratio between two HbA<sub>1c</sub> profiles*

According to Equation 1 and 2, the hazard ratio of the HbA<sub>1c</sub> profile  $x_1$  vs  $x_0$  at time  $t$  is given by

$$HR(t) = \frac{e^{\beta_5 \int_0^t x_1(s)g(t-s)ds}}{e^{\beta_5 \int_0^t x_0(s)g(t-s)ds}} = e^{\beta_5 \int_0^t (x_1(s)-x_0(s))g(t-s)ds}. \quad (Eq. 4)$$

If  $x_1(s) = x_0(s) + z$  for all  $s \in [0, T]$  and some constant  $z$ , i.e. for a constant shift in HbA<sub>1c</sub>, Equation 4 simplifies to

$$HR(t) = e^{\beta_5 z \int_0^t g(s)ds}. \quad (Eq. 5)$$

In particular, the hazard ratio for a constant shift in HbA<sub>1c</sub> is independent of the reference HbA<sub>1c</sub> profile  $x_0$ . If, on the other hand,  $x_1$  is given by

$$x_1(s) = x_0(s) + z \times \mathbf{1}_{(s>t_0)} = \begin{cases} x_0(s), & s \leq t_0 \\ x_0(s) + z, & s > t_0 \end{cases}$$

i.e. the shift is imposed first at time  $t_0$ , the hazard ratio function becomes

$$HR(t) = \begin{cases} 1, & t \leq t_0 \\ e^{\beta_5 z \int_0^{t-t_0} g(s)ds}, & t > t_0 \end{cases}. \quad (Eq. 6)$$

The cumulative weight ascribed to HbA<sub>1c</sub> values the first  $s$  years after diagnosis to the effect of HbA<sub>1c</sub> on the hazard  $t$  years after diagnosis is given by

$$\frac{\int_{t-s}^t g(u)du}{\int_0^t g(u)du}. \quad (Eq. 7)$$

#### *Relative risk between two HbA<sub>1c</sub> profiles*

The survival function  $S(t) := Prob(\text{No event before time } t)$  can be calculated from the hazard function  $\lambda(t)$  according to the formula

$$S(t) = e^{-\Lambda(t)} \approx 1 - \Lambda(t), \quad (Eq. 8)$$

where

$$\Lambda(t) = \int_0^t \lambda(s)ds$$

is the cumulative hazard function. The approximation in Equation 8 follows from a Taylor expansion of the exponential function and is appropriate for events with low probabilities.

The risk of an event in a time interval  $[s, t]$  from  $s$  to  $t$  years after diagnosis is thus given by

$$\begin{aligned} Prob(\text{Event time in interval } [s, t]) &= 1 - S(t) - (1 - S(s)) \approx \Lambda(t) - \Lambda(s) \\ &= \int_s^t \lambda(u)du. \quad (Eq. 9) \end{aligned}$$

The absolute risk depends on all the covariates in the model and on the time interval of interest. Considering two different patient and HbA<sub>1c</sub> profiles, the relative risk of an event in the time interval  $[s, t]$  can be calculated as the ratio of corresponding absolute risks obtained from Equation 9, i.e.

$$\frac{\int_s^t \lambda_1(u)du}{\int_s^t \lambda_0(u)du}, \quad (Eq. 10)$$

where  $\lambda_1(u)$  and  $\lambda_0(u)$  are the corresponding hazard functions. Keeping the other covariates fixed, the relative risk due to differences in two HbA<sub>1c</sub> curves  $x_1$  and  $x_0$  becomes a function of the time since diagnosis, reference HbA<sub>1c</sub> profile  $x_0$  and hazard ratio function  $HR(t)$  (Equation 4) between the two HbA<sub>1c</sub> profiles. When evaluating the relative risks associated

with various HbA<sub>1c</sub> profiles we found the relative risk to be essentially independent of the reference HbA<sub>1c</sub> profile  $x_0$ , motivating the approximation

$$\frac{1}{t-s} \int_s^t HR(u) du \quad (Eq. 11)$$

of the relative risk of an event in a time interval  $[s, t]$ .

### **Parameter estimation and hypothesis testing**

Estimation was performed using maximum likelihood, where the parameters  $b_1, b_2$  and  $b_3$  were estimated simultaneously with the regression coefficients  $\beta_1, \dots, \beta_5$ ; a possibility offered by the use of Poisson regression instead of e.g. Cox regression. The significance of individual regression coefficients was assessed by likelihood ratio tests, and corresponding confidence intervals were computed by test inversion. Estimates and confidence intervals for the hazard ratio of the influence weighted HbA<sub>1c</sub> variable at various follow-up times and for the relative risk associated with early and late HbA<sub>1c</sub> reductions were computed from the corresponding regression coefficient (wHbA<sub>1c</sub>, Table S1), fixing the parameters of the HbA<sub>1c</sub> weight function  $g(t)$  at their estimated values.

## Article II. Tables

**Table S1.** Estimated parameters with 95% confidence intervals for the variables included in the final model (Equation 1).

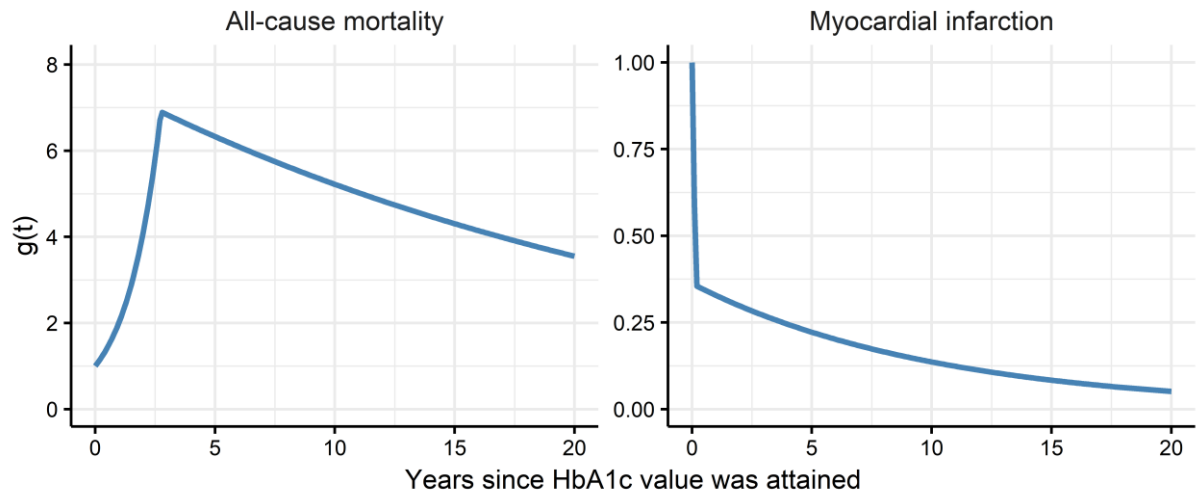
Variable		Parameter estimate (95% CI)	
		All-cause mortality	Myocardial infarction
Regression coefficients	Intercept	-9.7094 (-9.510 – -9.935)	-7.4416 (-7.692 – -7.223)
	Current diabetes duration (years)	-0.1318 (-0.152 – -0.114)	-0.1275 (-0.1537 – -0.1052)
	Current age (years)	0.09953 (0.0962 – 0.1024)	0.0641 (0.0602 – 0.0675)
	Sex (male = 1, female = 2)	-0.53154 (-0.6846 – -0.3785)	-0.7239 (-0.8968 – -0.5510)
	wHbA <sub>1c</sub>	0.0032475 (0.0027 – 0.0037)	0.0832 (0.0682 – 0.0960)
Weight function $g(t)$	$b_1$	0.704737 (0.638 – 0.755)	-5.2662 (-6.310 – -4.507)
	$b_2$	2.7417 (2.47 – 2.95)	0.1967 (0.1673 – 0.2377)
	$b_3$	-0.03853 (-0.080 – -0.012)	0.1967 (0.1673 – 0.2377)
<p>wHbA<sub>1c</sub> is the influence weighted HbA<sub>1c</sub> variable (Equation 2) using the influence (weight) function <math>g(t)</math> (Equation 3).</p> <p><math>b_1</math> describes the initial increasing/decreasing phase of the function <math>g(t)</math>.</p> <p><math>b_2</math> is the breakpoint of the piecewise exponential function <math>g(t)</math>.</p> <p><math>b_3</math> describes the increase/decrease of the function <math>g(t)</math> after the breakpoint <math>b_2</math>.</p> <p>CI, confidence interval; HbA<sub>1c</sub>, Hemoglobin A<sub>1c</sub>.</p>			

**Table S2.** Estimated relative risks of all-cause mortality and myocardial infarction between 0–10, 10–15 and 10–20 years after diagnosis assuming 0.5 or 2 percentage units (5.5 or 22 mmol/mol) lower HbA<sub>1c</sub> from diagnosis, and when the same HbA<sub>1c</sub> lowering was imposed from 5 and from 10 years after diagnosis.

Years after diagnosis	Relative risk (95% CI) <i>per 0.5 percentage units lower HbA<sub>1c</sub></i>			Relative risk (95% CI) <i>per 2 percentage units lower HbA<sub>1c</sub></i>		
	HbA <sub>1c</sub> lowered at diagnosis	HbA <sub>1c</sub> lowered 5 years after diagnosis	HbA <sub>1c</sub> lowered 10 years after diagnosis	HbA <sub>1c</sub> lowered at diagnosis	HbA <sub>1c</sub> lowered 5 years after diagnosis	HbA <sub>1c</sub> lowered 10 years after diagnosis
<b>All-cause mortality</b>						
<b>0–10</b>	0.963 (0.958 - 0.969)	0.993 (0.992 - 0.995)	1.00	0.864 (0.847 - 0.884)	0.973 (0.970 - 0.977)	1.00
<b>10–15</b>	0.902 (0.889 - 0.917)	0.941 (0.933 - 0.950)	0.987 (0.985 - 0.989)	0.660 (0.623 - 0.705)	0.782 (0.756 - 0.814)	0.946 (0.939 - 0.955)
<b>10–20</b>	0.886 (0.871 - 0.903)	0.921 (0.910 - 0.933)	0.963 (0.958 - 0.969)	0.616 (0.576 - 0.665)	0.721 (0.689 - 0.759)	0.864 (0.847 - 0.884)
<b>Myocardial infarction</b>						
<b>0–10</b>	0.945 (0.936 - 0.954)	0.984 (0.981 - 0.987)	1.00	0.799 (0.772 - 0.831)	0.937 (0.929 - 0.948)	1.00
<b>10–15</b>	0.896 (0.881 - 0.914)	0.923 (0.911 - 0.936)	0.967 (0.962 - 0.973)	0.644 (0.602 - 0.697)	0.723 (0.688 - 0.767)	0.875 (0.857 - 0.896)
<b>10–20</b>	0.888 (0.872 - 0.907)	0.909 (0.896 - 0.925)	0.945 (0.936 - 0.954)	0.622 (0.578 - 0.677)	0.683 (0.645 - 0.732)	0.799 (0.772 - 0.831)
The relative risk of an event in a time interval 0–10, 10–15 or 10–20 years after diagnosis was calculated according to Equation 11. CI, confidence interval; HbA <sub>1c</sub> , Hemoglobin A <sub>1c</sub> .						

### Article III. Figures

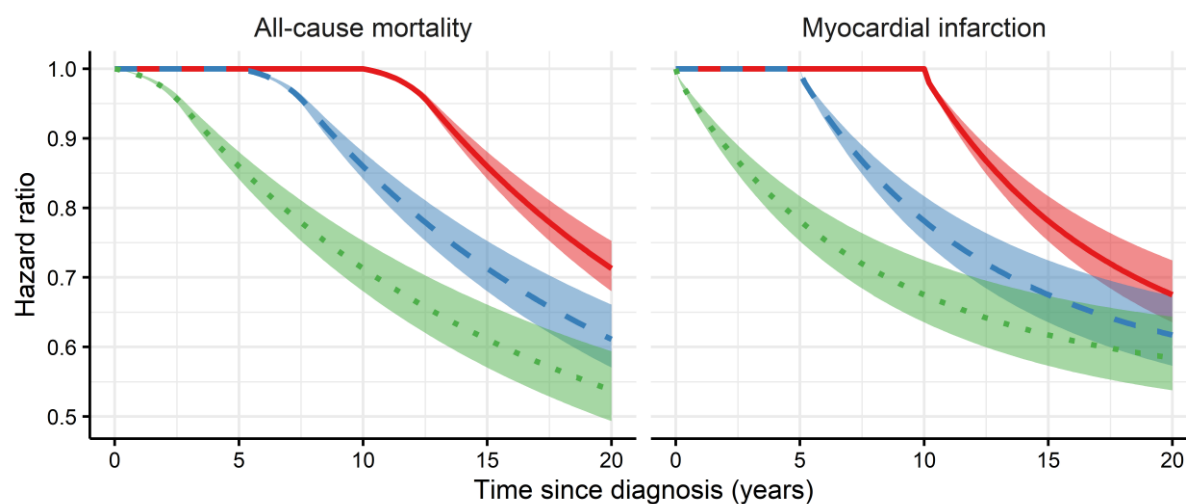
**Figure S1.** Estimated weight function  $g(t)$  (Equation 3) of the influence weighted HbA<sub>1c</sub> variable (Equation 2) when analysing the time dependent effects of HbA<sub>1c</sub> on all-cause mortality (left) and myocardial infarction (right). The corresponding estimates of the parameters  $b_1$ ,  $b_2$  and  $b_3$  are provided in Table S1.



**Figure S2.** Time-dependent hazard ratios for all cause-mortality (left) and myocardial infarction (right) from 0 to 20 years after diagnosis of type 2 diabetes assuming a 0.5-percentage unit lower  $HbA_{1c}$  from diagnosis (green dotted lines), and when the same  $HbA_{1c}$  lowering was imposed from 5 years (blue dashed lines) and from 10 years (red solid lines) after diagnosis. The shaded regions represent 95% confidence limits. Hazard ratios were calculated according to Equation 6.



**Figure S3.** Time-dependent hazard ratios for all cause-mortality (left) and myocardial infarction (right) from 0 to 20 years after diagnosis of type 2 diabetes assuming a 2-percentage unit lower HbA<sub>1c</sub> from diagnosis (green dotted lines), and when the same HbA<sub>1c</sub> lowering was imposed from 5 years (blue dashed lines) and from 10 years (red solid lines) after diagnosis. The shaded regions represent 95% confidence limits. Hazard ratios were calculated according to Equation 6.



**Figure S4.** Cumulative number of events for observed and model predicted all-cause mortality (left) and myocardial infarction (right) during follow-up.

