Supplementary Appendix

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

Supplement to:

Historical HbA_{1c} Values May Explain the Type 2 Diabetes Legacy Effect: UKPDS 88

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Contents

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_{1c} 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_{1c} 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 λ is the hazard. In each time interval, the hazard $\lambda(t)$ at time t was modelled as

$$\log(\lambda(t)) = \beta_1 + \beta_2 \times A\text{ge}(\tau) + \beta_3 \times \text{Diabetes duration}(\tau) + \beta_4 \times \text{Sex} + \beta_5 \times w\text{HbA1c}(\tau), \quad (Eq.1)$$

where $A\text{ge}(\tau)$, $\text{Diabetes duration}(\tau)$ and $w\text{HbA1c}(\tau)$ are the age, diabetes duration and influence weighted HbA_{1c} at time $\tau = 0.2 \times \lfloor 5t \rfloor$, i.e. evaluated at the left endpoint of the current time interval. The influence weighted HbA_{1c} variable was defined as an integral of historical HbA_{1c} values

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

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

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

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_{1c} 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_{1c} hazard ratios and relative risks

Consider two continuous HbA_{1c} 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_{1c} values at the time point $s \in [0,T]$. We describe below how hazard ratios and relative risks of the HbA_{1c} 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_{1c} profiles

According to Equation 1 and 2, the hazard ratio of the HbA_{1c} 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_{1c}, 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_{1c} is independent of the reference HbA_{1c} profile x_0. If, on the other hand, x_1 is given by

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

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

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

The cumulative weight ascribed to HbA_{1c} values the first s years after diagnosis to the effect of HbA_{1c} 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_{1c} 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

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

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

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

The absolute risk depends on all the covariates in the model and on the time interval of interest. Considering two different patient and HbA_{1c} 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_{1c} curves x_1 and x_0 becomes a function of the time since diagnosis, reference HbA_{1c} profile x_0 and hazard ratio function $HR(t)$ (Equation 4) between the two

HbA_{1c} profiles. When evaluating the relative risks associated with various HbA_{1c} profiles we found the relative risk to be essentially independent of the reference HbA_{1c} 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 $\beta_1, \ldots, \beta_5$; 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_{1c} variable at various follow-up times and for the relative risk associated with early and late HbA_{1c} reductions were computed from the corresponding regression coefficient ($wHbA_{1c}$, Table S1), fixing the parameters of the HbA_{1c} weight function $g(t)$ at their estimated values.

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$_{1c}$	0.0032475 (0.0027 – 0.0037)	0.0832 (0.0682 – 0.0960)
Weight function $g(t)$	$\boldsymbol{b_1}$	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)***
	$\boldsymbol{b_3}$	-0.03853 (-0.080 – -0.012)	0.1967 (0.1673 – 0.2377)

wHbA$_{1c}$ is the influence weighted HbA$_{1c}$ variable (Equation 2) using the influence (weight) function $g(t)$ (Equation 3).
b_1 describes the initial increasing/decreasing phase of the function $g(t)$.
b_2 is the breakpoint of the piecewise exponential function $g(t)$.
b_3 describes the increase/decrease of the function $g(t)$ after the breakpoint b_2.
CI, confidence interval; HbA$_{1c}$, Hemoglobin A$_{1c}$.

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_{1c} from diagnosis, and when the same HbA_{1c} lowering was imposed from 5 and from 10 years after diagnosis.

Years after diagnosis	Relative risk (95% CI) *per* 0.5 percentage units lower HbA_{1c}			Relative risk (95% CI) *per* 2 percentage units lower HbA_{1c}		
	HbA_{1c} lowered at diagnosis	HbA_{1c} lowered 5 years after diagnosis	HbA_{1c} lowered 10 years after diagnosis	HbA_{1c} lowered at diagnosis	HbA_{1c} lowered 5 years after diagnosis	HbA_{1c} lowered 10 years after diagnosis
All-cause mortality						
0–10	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
10–15	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)
10–20	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)
Myocardial infarction						
0–10	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
10–15	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)
10–20	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_{1c}, Hemoglobin A_{1c}.

Figures

Figure S1. Estimated weight function $g(t)$ (Equation 3) of the influence weighted HbA_{1c} variable (Equation 2) when analysing the time dependent effects of HbA_{1c} 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.

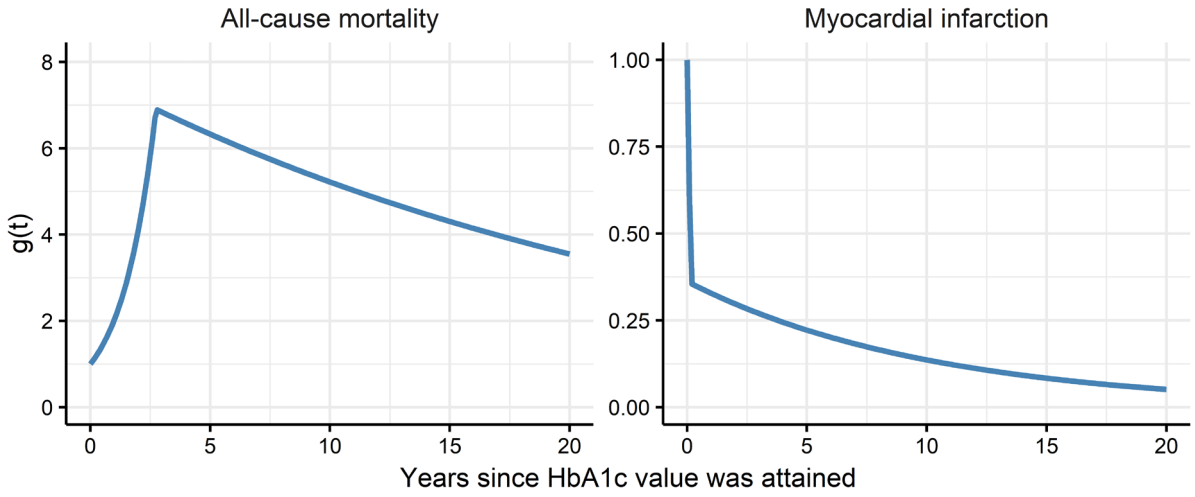

Figure S2. Time-dependent hazard ratios for all cause-mortality (left) and myocardial infarction (right) from 0 to 20 years after diagnosis of type 2 diabetes assuming a 0.5-percentage unit lower HbA_{1c} from diagnosis (green dotted lines), and when the same HbA_{1c} lowering was imposed from 5 years (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.

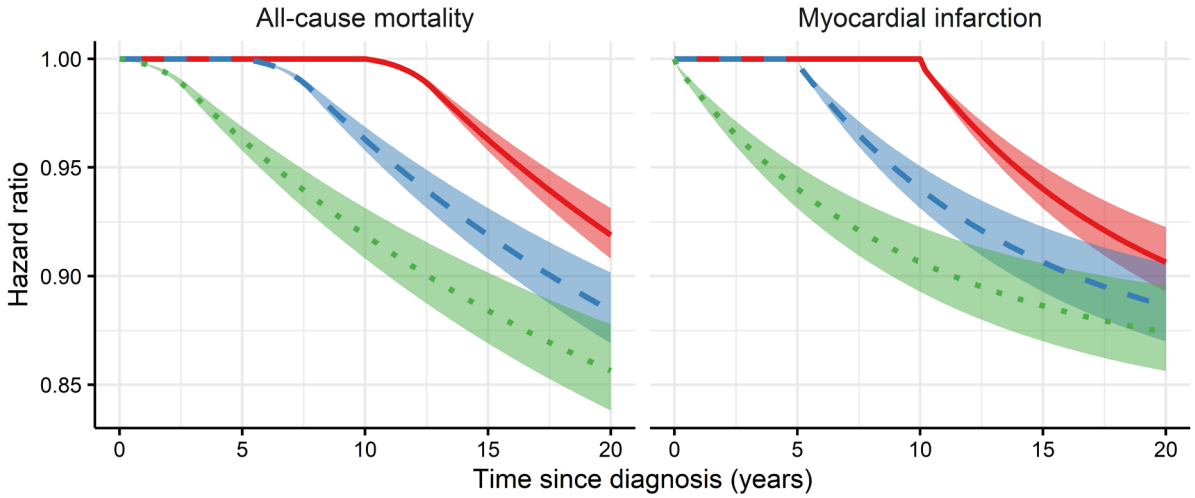

Figure S3. Time-dependent hazard ratios for all cause-mortality (left) and myocardial infarction (right) from 0 to 20 years after diagnosis of type 2 diabetes assuming a 2-percentage unit lower HbA_{1c} from diagnosis (green dotted lines), and when the same HbA_{1c} lowering was imposed from 5 years (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.

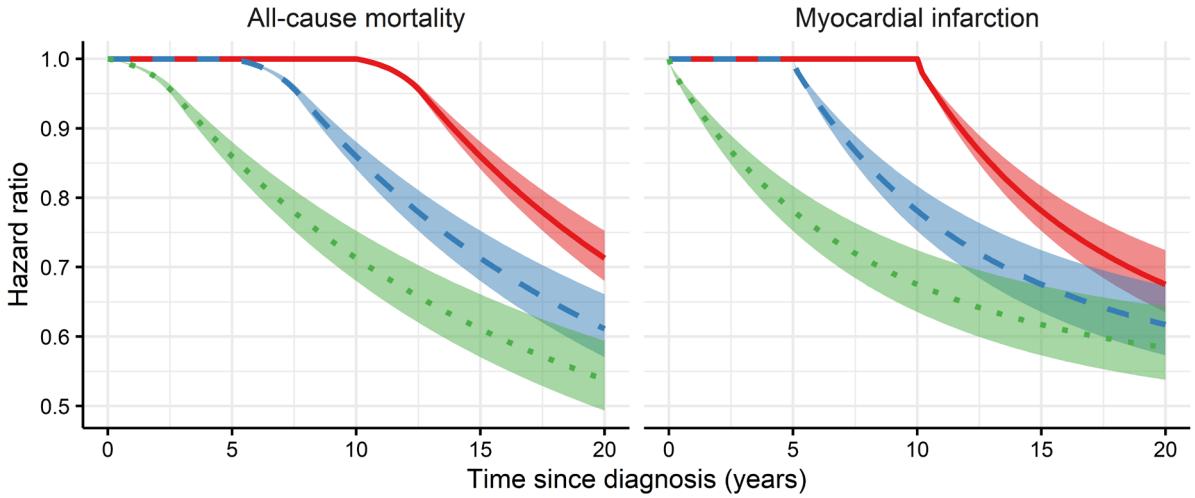

Figure S4. Cumulative number of events for observed and model predicted all-cause mortality (left) and myocardial infarction (right) during follow-up.