

Risk Factors for Cardiovascular Disease in Type 1 Diabetes

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This Appendix presents supplemental materials cited in the text of the main manuscript.

Model Selection

The final models for Any-CVD and MACE presented in Table 4 of the main manuscript were obtained in a forward fashion by sequentially considering the blocks of variables described in Supplementary Table 1 herein. The models were also confirmed in two sensitivity analyses that started with all variables from all blocks.

Three statistical methods were employed for variable selection/deletion. One approach simply fit a Cox PH model and deleted factors that were not statistically significant. Another approach conducted a search for the best subset model based on the minimum (best) Akaike Information Criterion (AIC) (17). A third identified covariate deletions by fitting a model with a penalized likelihood “lasso” (least absolute shrinkage and selection operator) method (18). The lasso shrinks the regression coefficients toward zero, and sets those deemed unimportant to zero (penalized). A model can then be fit with the remaining selected variables.

For the final models, the forward variable selection approach started with the variables in the Design block in Table 1, namely cohort and treatment group, and the three approaches were applied. First, a Cox model that included both variables was fit, and a variable was selected for inclusion if its p-value was below a certain cut-off value (0.10 was used herein). Second, a penalized likelihood model was fit using both variables, and those with non-zero coefficients were retained. Third, a search identified the sub-model with the lowest AIC value, and the variables included in that model were retained. A risk factor was retained if it met at least one of the three criteria. From the Design block, both cohort and treatment group were selected (e.g., they both had p-values less than 0.10).

At the next step, the variables in the next block, in this case the Demographic-Physical block (such as gender, age, weight and BMI), were added to the previously selected variables (i.e., cohort and treatment group). The three variable selection criteria were applied to this set of variables, all of them, not just those added; and again, variables that met at least one criterion were selected, and the others were dropped. This could include deletion of variables entered in preceding blocks.

The procedure continued in a similar fashion by adding each block to the already selected risk factors, and variables selected by at least one criterion were kept in the model, while the others were dropped. After the final block (Glycemia) was considered, the remaining set of variables that were considered of interest were employed in a Cox model, and variables that did not reach statistical significance at level 0.05 were then dropped to yield the final model.

Two sensitivity analyses were conducted to confirm the final model, and they both started with all variables in all blocks. The first approach was to fit a penalized Cox model to identify variables to be deleted (those with a zero coefficient), followed by a Cox model using only the variables that were retained (had non-zero coefficients). The second method identified the sub-model with the lowest AIC, and then fit a Cox model using only the variables selected by the AIC criterion. Both approaches led to the same set of significant variables as obtained using the forward selection procedure shown in Table 4.

SUPPLEMENTARY DATA

Supplementary Table 1. CVD risk factors (by block) employed in the analyses with a description of availability.

Block	Variable	Availability*
<u>DESIGN</u>		
	Cohort	B
	Treatment Group	B
<u>DEMOGRAPHIC</u>		
Physical	Gender (male versus female)	B
	Age (yr)	B
	Adult	B
	Weight (kg)	B, C [†] , M [†]
	Weight Gain (kg)	C [†]
	Body mass index (kg/m ²)	B, C [†] , M [†]
Behavioral	Current cigarette smoker	B, C [†]
	Occasional or regular drinker	B, C [†]
	Moderate or strenuous activity	B, C [†]
Family History	Family history	
	Hypertension	B
	Myocardial infarction	B
	Type 1 Diabetes	B
	Type 2 Diabetes	B
<u>TRADITIONAL</u>		
Blood pressure	Systolic (mm Hg)	B, C [†] , M [†]
	Diastolic (mm Hg)	B, C [†] , M [†]
	Pulse pressure (mm Hg)	B, C [†]
	Pulse rate (bpm)	B, C [†] , M [†]
	Hypertension (>140/90 or medication)	B, C [†] , A [†]
Medications	ACE	C [‡]
	ARB	C [‡]
	Beta Blockers	C [‡]
	Calcium Channel Blockers	C [‡]
	Lipid Lowering	C [‡]
Lipids	Total cholesterol (mg/dl)	B, C [§] , M [§]
	Triglycerides (mg/dl)	B, C [§] , M [§]
	HDL cholesterol (mg/dl)	B, C [§] , M [§]
	LDL cholesterol (mg/dl)	B, C [§] , M [§]
	Hyperlipidemia (LDL > 130 or medication)	B, C [§]
<u>DIABETES-RELATED</u>		
History	Duration of diabetes (yr)	B
	Stimulated C-peptide (nmol/L)	B
	Duration <60 months	
	Duration ≥60 months	
	Insulin dose (units/kg/day)	B, C [†] , M [†]
	eGlucose Disposal Rate	C [‡]

SUPPLEMENTARY DATA

Nephropathy	eGFR (mL/min per 1.73 m ²)	B, C [†]
	eGFR<60	C [†] , A [†]
	AER (mg/24 hr)	B, C [§] ,
	AER ≥40 mg/24 hr,	A [§]
	AER≥300 mg/24 hr, Sustained AER≥30 mg/24 hr	A [§]
Hypoglycemia	Coma and/or seizure	B, C [†]
	Requiring assistance	B, C [†]
Glycemia	HbA1c (%)	B, C [†] , M [†]

* A=Cumulative Incidence (such as Any Use), B=Baseline Value, C=Current Value, M=Updated Mean Value. Categories C, M and A enter the analyses as time dependent covariates.

[†]Collected annually during DCCT and EDIC

[‡]Collected annually in EDIC, not collected in DCCT

[§]Collected annually in DCCT, every two years in EDIC

SUPPLEMENTARY DATA

Supplementary Table 2. Median and inter-quartile range or prevalence (%) for fixed baseline characteristics of DCCT/EDIC participants according to the presence or absence of MACE over the course of the DCCT/EDIC study, and the corresponding hazard ratio of any CVD per unit change in the baseline covariate.

	MACE			HR	95% CI	p-value
	Overall	No	Yes			
DESIGN						
Treatment group (% conventional)	51	50	56	1.302	(0.855, 1.984)	0.2184
Cohort (% secondary)	50	49	64	1.603	(1.036, 2.479)	0.0341
DEMOGRAPHIC						
Physical						
Gender (% men)	53	52	58	1.293	(0.847, 1.975)	0.234
Age (yr)	27 (22,32)	27 (22,32)	32 (28,36)	1.112	(1.074, 1.151)	0
Adult vs. adolescent (< 18 years)	86	86	97	5.044	(1.591, 15.992)	0.006
Weight Men (kg)	74 (67,82)	74 (67,82)	76 (69,82)	1.001	(0.976, 1.026)	0.9579
Weight Women (kg)	62 (56,69)	61 (56,68)	64 (58,70)	1.04	(1.005, 1.076)	0.0244
BMI Men (kg/m ²)	24 (22,25)	24 (22,25)	24 (22,25)	1.034	(0.938, 1.14)	0.4975
BMI Women (kg/m ²)	23 (21,25)	23 (21,25)	24 (22,26)	1.108	(0.996, 1.232)	0.0586
Behavioral						
Smoking (%)	19	17	38	2.927	(1.901, 4.508)	0
Alcohol (% occasional or regular)	22	22	16	0.692	(0.391, 1.226)	0.2073
Exercise (% moderate or strenuous)	70	70	75	1.259	(0.777, 2.041)	0.3495
Family History						
Family history of HT (%)	56	56	53	0.9	(0.592, 1.368)	0.6218
Family history of MI (%)	49	48	55	1.251	(0.822, 1.903)	0.2964
Family history of T1D (%)	14	14	18	1.376	(0.801, 2.365)	0.2481
Family history of T2D (%)	9	9	9	1.025	(0.495, 2.12)	0.9473
TRADITIONAL						
Blood Pressure						
Systolic (mm Hg)	114 (106,122)	114 (106,122)	113 (108,126)	1.013	(0.995, 1.031)	0.1618
Diastolic (mm Hg)	72 (68,80)	72 (68,80)	76 (68,80)	1.021	(0.997, 1.046)	0.0854
Pulse pressure (mm Hg)	40 (34,48)	40 (35,48)	40 (34,48)	1.001	(0.98, 1.023)	0.9303
Pulse rate (bpm)	76 (68,84)	76 (68,82)	80 (74,88)	1.025	(1.008, 1.043)	0.0042

SUPPLEMENTARY DATA

Lipids						
Total cholesterol (mg/dl)	174 (153,197)	173 (152,196)	184 (160,207)	1.011	(1.005, 1.017)	3.00E-04
Triglycerides (mg/dl)	73 (55,94)	72 (55,93)	84 (59,105)	1.981	(1.291, 3.04)	0.0017
HDLc (mg/dl)	49 (42,57)	50 (42,57)	45 (41,58)	0.988	(0.97, 1.006)	0.1864
LDLc (mg/dl)	107 (91,127)	106 (90,126)	119 (98,137)	1.013	(1.006, 1.02)	2.00E-04
DIABETES-RELATED						
History						
Duration of Diabetes (months)	49 (26,108)	48 (26,106)	70 (30,134)	1.005	(1.001, 1.009)	0.0238
C-peptide (nmol/L)*						
Diabetes duration <5 years	0.13 (0.04,0.25)	0.13 (0.04,0.25)	0.12 (0.03,0.24)	0.441	(0.039, 5.025)	0.5097
Duration ≥5 years	0.03 (0.03,0.04)	0.03 (0.03,0.04)	0.03 (0.03,0.03)	<0.001	(0, 7.958)	0.1094
Nephropathy						
Log AER (mg/24 hr)	2.4 (2,2.9)	2.4 (2,2.9)	2.6 (1.8,2.9)	1.087	(0.837, 1.411)	0.5328
Glycemia						
HbA1c [% (mmol/mol)]	8.8 (7.8,10.1)	8.8 (7.8,10.1)	9.3 (8.1,10.7)			
	73 (62,87)	73 (62,87)	78 (65,93)	1.168	(1.037, 1.316)	0.0106

ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blockers; BMI=body mass index; HT=hypertension; MI=myocardial infarction; T1D=type 1 diabetes; T2D=type 2 diabetes; HDLc=high-density lipoprotein cholesterol; LDLc=low-density lipoprotein cholesterol; AER=albumin excretion rate

Data are median (first quartile, third quartile) or %.

*C-peptide is presented separately within diabetes duration strata because the eligibility range differed among those ≤ 5 years duration (0 – 0.5 nmol/L) and those > 5 years (0 – 0.2 nmol/L).

SUPPLEMENTARY DATA

Supplementary Table 3. Median and inter-quartile range or prevalence (%) for time-dependent characteristics of DCCT/EDIC participants at DCCT baseline and at 10, 20 and 25 years of follow-up for those at risk of any cardiovascular disease over the course of the DCCT/EDIC study. The covariate type is also indicated, M = the updated mean value over follow-up, C = the current or most recent covariate value.

	Type	Baseline	Year 10	Year 20	Year 25
N		1441	1380	1235	988
DEMOGRAPHIC					
Physical					
Age (yr)	C	27 (22,32)	36 (31,42)	46 (41,51)	51 (45,56)
Weight Men (kg)	C	74 (67,82)	83 (76,92)	90 (80,100)	90 (80,101)
Weight Women (kg)	C	62 (56,69)	69 (62,78)	73 (65,84)	73 (65,84)
Mean BMI(kg/m ²)	M	23 (21,25)	25 (23,27)	26 (24,28)	26 (24,29)
BMI Men (kg/m ²)	C	24 (22,25)	26 (24,29)	28 (25,31)	28 (25,31)
BMI Women (kg/m ²)	C	23 (21,25)	25 (23,28)	27 (24,31)	27 (24,31)
Behavior					
Smoking (%)	C	19	19	14	13
Alcohol (% occasional or regular)	C	22	41	46	45
Exercise (% moderate or strenuous)	C	70	55	55	56
TRADITIONAL					
Blood Pressure					
Systolic (mm Hg)	C				
	C	114 (106,122)	118 (110,126)	120 (111,129)	120 (110,130)
Mean Systolic (mm Hg)	M	114 (106,122)	115 (110,121)	118 (112,124)	118 (112,124)
Diastolic (mm Hg)	C	72 (68,80)	76 (70,82)	74 (68,80)	71 (65,78)
Mean Diastolic (mm Hg)	M	72 (68,80)	74 (71,78)	75 (71,78)	74 (71,77)
Pulse					
Pulse pressure (mm Hg)	C	40 (34,48)	42 (36,50)	46 (39,53)	48 (41,56)
Pulse rate (bpm)	C	76 (68,84)	72 (68,80)	72 (64,80)	70 (63,78)
Mean Pulse rate (bpm)	M	76 (68,84)	74 (69,78)	73 (69,77)	73 (69,77)

SUPPLEMENTARY DATA

Hypertension (%)	A	3	19	56	64
Hypertension Cumulative (%)	C	0	23	70	79
Medications					
ACE (%)	C	0	7	39	43
ARB (%)	C	0	0	12	16
Beta Blockers (%)	C	0	1	4	9
Calcium Channel Blockers (%)	C	0	1	5	8
Lipid Lowering (%)	C	0	3	43	59
Lipids					
Total cholesterol (mg/dl)	C	174 (153,197)	184 (161,207)	177 (155,200)	172 (149,195)
Mean Total cholesterol (mg/dl)	M	174 (153,197)	181 (163,202)	183 (165,199)	181 (165,196)
Triglycerides (mg/dl)	C	70 (55,94)	73 (54,104)	71 (51,104)	65 (50,91)
Mean Triglycerides (mg/dl)	M	70 (52,93)	73 (59,97)	74 (59,99)	74 (59,97)
HDLc (mg/dl)	C	49 (42,57)	52 (44,62)	53 (45,65)	59 (49,72)
Mean HDLc (mg/dl)	M	49 (42,57)	50 (44,59)	53 (45,61)	53 (46,63)
LDLc (mg/dl)	C	107 (91,127)	113 (93,135)	103 (86,123)	94 (77,111)
Mean LDLc (mg/dl)	M	107 (91,127)	112 (96,131)	112 (97,127)	108 (95,121)
Hyperlipidemia (%)	C	23	30	55	65
DIABETES-RELATED					
History					
Insulin Dose (units/kg/day)	C	0.64 (0.5,0.8)	0.63 (0.51,0.76)	0.54 (0.36,0.69)	0.51 (0.33,0.69)
Mean Insulin Dose (units/kg/day)	M	0.64 (0.5,0.8)	0.65 (0.55,0.79)	0.61 (0.5,0.72)	0.59 (0.49,0.71)
Estimated Glucose Disposal Rate	C	NA (NA,NA)	9 (7,10)	7 (5,9)	6 (5,8)
Nephropathy					
Estimated GFR (mL/min per 1.73 m ²)	C	125 (118,134)	113 (105,120)	101 (90,110)	96 (86,105)
eGFR<60 (%)	C	0	0	3	5
Any eGFR<60 (%)	A	0	0	4	7
Log AER (mg/24 hr)	C	2.4 (2,3.9)	2.3 (1.8,3)	2.4 (2,3.1)	2.4 (2,3.1)

SUPPLEMENTARY DATA

Sustained AER \geq 30 (%)	C	5	13	16	15
AER \geq 40 (%)	C	5	13	16	16
AER \geq 300 (%)	C	0	3	6	6
Any AER \geq 40 (%)	A	5	28	38	44
Any AER \geq 300 (%)	A	0	4	9	10
Hypoglycemia					
Coma/Seizure (%)	C	0	9	19	14
Requiring Assistance (%)	C	0	34	46	43
Glycemia					
HbA1c [% (mmol/mol)]	C	8.8 (7.8,10.1) 73 (62,87)	8.1 (7.3,9.1) 65 (56,76)	7.7 (7.0,8.6) 61 (53,70)	7.8 (7.1,8.5) 62 (54,69)
Mean HbA1c [% (mmol/mol)]	M	8.8 (7.8,10.1) 73 (62,87)	8.0 (7.2,9.0) 64 (54,75)	7.9 (7.3,8.6) 63 (56,70)	7.9 (7.3,8.5) 63 (56,69)

BMI=body mass index; ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blockers; HDLc=high-density lipoprotein cholesterol; LDLc=low-density lipoprotein cholesterol; GFR=glomerular filtration rate; AER=albumin excretion rate

*C=Current (or most recent) value, M=Updated mean value, A=Cumulative Incidence (such as Any Use). Categories C, M, and A correspond to time-dependent covariates assessed or measured at or most recently prior to each event time or right censoring time, i.e. at the most recent visit up to the particular time-point.

Data are median (first quartile, third quartile) or %. For each time-dependent covariate, average value (and quartiles) are computed from all values over the entire period of follow-up to the event time (any CVD “yes”) or censoring (any CVD “no”). Only subjects at risk at the particular time-point were included; for example, at year 10 there were 1380 active participants without a prior CVD event. The number at risk beyond year 24 declines owing to staggered entry of participants into the DCCT during 1983-1989, only 37 being at risk of any CVD in year 30.

SUPPLEMENTARY DATA

Supplementary Table 4. Median and inter-quartile range or prevalence (%) for time-dependent characteristics of DCCT/EDIC participants at DCCT baseline and at 10, 20 and 25 years of follow-up for those at risk of MACE over the course of the DCCT/EDIC study, and the corresponding hazard ratio of any CVD per unit change in the covariate.

	Baseline	Year 10	Year 20	Year 25	HR	95% CI	p-value
N	1441	1391	1292	1058			
DEMOGRAPHIC							
Physical							
Age (yr)	27 (22,32)	36 (31,42)	46 (41,51)	51 (46,56)	1.112	(1.074, 1.151)	0
Weight Men (kg)	74 (67,82)	83 (76,92)	90 (80,100)	90 (80,101)	0.984	(0.964, 1.004)	0.1092
Weight Women (kg)	62 (56,69)	69 (62,78)	73 (65,84)	74 (65,84)	1.008	(0.988, 1.028)	0.4519
Mean BMI (kg/m ²)	23 (21,25)	25 (23,27)	26 (24,29)	26 (24,29)	1.009	(0.952, 1.069)	0.758
BMI Men (kg/m ²)	24 (22,25)	26 (24,29)	28 (25,31)	28 (25,31)	0.966	(0.903, 1.034)	0.3216
BMI Women (kg/m ²)	23 (21,25)	25 (23,28)	27 (24,31)	27 (24,31)	1.019	(0.962, 1.08)	0.5147
Behavior							
Smoking (%)	19	19	14	12	2.247	(1.411, 3.579)	7.00E-04
Alcohol (% occasional or regular)	22	40	45	45	0.783	(0.608, 1.007)	0.0568
Exercise (% moderate or strenuous)	70	55	55	55	0.979	(0.676, 1.416)	0.909
TRADITIONAL							
Blood Pressure							
Systolic (mm Hg)	114 (106,122)	118 (110,126)	120 (112,129)	120 (110,130)	1.034	(1.022, 1.046)	0
Mean Systolic (mm Hg)	114 (106,122)	115 (110,121)	118 (112,124)	118 (112,124)	1.071	(1.046, 1.096)	0
Diastolic (mm Hg)	72 (68,80)	76 (70,82)	74 (68,80)	71 (65,78)	1.01	(0.987, 1.034)	0.3842
Mean Diastolic (mm Hg)	72 (68,80)	74 (71,78)	75 (71,78)	74 (71,77)	1.044	(1.005, 1.085)	0.027
Pulse pressure (mm Hg)	40 (34,48)	42 (36,50)	46 (39,54)	48 (41,57)	1.045	(1.03, 1.059)	0
Hypertension (%)	3	19	58	65	2.198	(1.348, 3.586)	0.0016
Any Hypertension (%)	0	23	71	79	2.291	(1.303, 4.027)	0.004
Pulse rate (bpm)	76 (68,84)	74 (68,80)	72 (64,80)	70 (62,78)	1.029	(1.011, 1.048)	0.0016
Mean Pulse rate (bpm)	76 (68,84)	74 (69,78)	73 (69,77)	73 (69,77)	1.074	(1.044, 1.106)	0
Medications							
ACE (%)	0	7	40	44	0.945	(0.583, 1.533)	0.8191
ARB (%)	0	0	12	16	1.024	(0.486, 2.158)	0.9495
Beta Blockers (%)	0	1	4	11	2.796	(1.441, 5.424)	0.0024

SUPPLEMENTARY DATA

Calcium Channel Blockers (%)	0	1	5	8	2.385	(1.216, 4.68)	0.0115
Lipid Lowering (%)	0	3	44	60	1.141	(0.696, 1.872)	0.6006
Lipids							
Total cholesterol (mg/dl)	174 (153,197)	184 (161,207)	177 (155,200)	171 (149,195)	1.011	(1.007, 1.016)	0
Mean Total cholesterol (mg/dl)	174 (153,197)	181 (163,202)	184 (165,200)	181 (165,197)	1.018	(1.011, 1.025)	0
Triglycerides (mg/dl)	70 (55,94)	73 (54,104)	71 (51,104)	66 (50,92)	2.522	(1.807, 3.518)	0
Mean Triglycerides (mg/dl)	70 (52,93)	74 (59,97)	74 (59,99)	74 (59,98)	2.923	(1.87, 4.568)	0
HDLc (mg/dl)	49 (42,57)	52 (44,62)	53 (45,65)	58 (48,72)	0.984	(0.97, 0.999)	0.0323
Mean HDLc (mg/dl)	49 (42,57)	50 (44,59)	53 (45,61)	53 (46,63)	0.983	(0.965, 1.002)	0.0754
LDLc (mg/dl)	107 (91,127)	113 (93,135)	103 (86,122)	93 (75,111)	1.014	(1.008, 1.019)	0
Mean LDLc (mg/dl)	107 (91,127)	112 (96,131)	112 (97,127)	109 (96,122)	1.02	(1.012, 1.029)	0
Hyperlipidemia (%)	23	30	56	67	1.647	(1.055, 2.571)	0.0282
DIABETES-RELATED							
History							
Insulin Dose (units/kg/day)	0.64 (0.5,0.8)	0.63 (0.51,0.75)	0.53 (0.36,0.69)	0.51 (0.33,0.69)	1.363	(0.694, 2.678)	0.3691
Mean Insulin Dose (units/kg/day)	0.64 (0.5,0.8)	0.65 (0.55,0.79)	0.61 (0.5,0.73)	0.59 (0.49,0.71)	1.296	(0.433, 3.874)	0.6431
Estimated Glucose Disposal Rate	NA (NA,NA)	9 (7,10)	7 (5,9)	6 (5,8)	0.763	(0.683, 0.853)	0
Nephropathy							
Estimated GFR (mL/min per 1.73 m ²)	125 (118,134)	113 (105,120)	101 (90,109)	96 (85,104)	0.978	(0.971, 0.986)	0
eGFR<60 (%)	0	0	3	5	4.356	(2.21, 8.586)	0
Any eGFR<60 (%)	0	1	4	7	3.949	(2.099, 7.429)	0
Log AER (mg/24 hr)	2.4 (2.0,2.9)	2.3 (1.9,3.0)	2.4 (2.0,3.1)	2.4 (2.0,3.2)	1.283	(1.151, 1.431)	0
Sustained AER ≥30 mg/dl (%)	5	14	16	16	1.916	(1.18, 3.109)	0.0085
AER ≥40 mg/dl (%)	5	13	16	17	2.171	(1.355, 3.478)	0.0013
AER ≥300 mg/dl (%)	0	3	6	6	3.028	(1.64, 5.593)	4.00E-04
Any AER ≥40 mg/dl (%)	5	28	39	45	1.729	(1.127, 2.654)	0.0122
Any AER ≥300 mg/dl (%)	0	4	10	10	3.072	(1.834, 5.148)	0
Hypoglycemia							
Coma/Seizure (%)	0	9	18	13	1.021	(0.835, 1.248)	0.8379
Requiring Assistance (%)	0	34	45	42	1.005	(0.905, 1.114)	0.9319
Glycemia							
HbA1c [% (mmol/mol)]	8.8 (7.8,10.1)	8.1 (7.3,9.1)	7.7 (7.0,8.6)	7.8 (7.1,8.6)	1.297	(1.139, 1.478)	1.00E-04

SUPPLEMENTARY DATA

	8.8 (7.8,10.1)	8.0 (7.2,9.0)	7.9 (7.3,8.6)	7.9 (7.3,8.6)		
Mean HbA1c [% (mmol/mol)]	73 (62,87)	64 (54,75)	63 (56,70)	63 (56,70)	1.539 (1.309, 1.808)	0

BMI=body mass index; ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blockers; HDLc=high-density lipoprotein cholesterol; LDLc=low-density lipoprotein cholesterol; GFR=glomerular filtration rate; AER=albumin excretion rate

*C=Current (or most recent) value, M=Updated mean value, A=Cumulative Incidence (such as Any Use). Categories C, M, and A correspond to time-dependent covariates assessed or measured at or most recently prior to each event time or right censoring time, i.e. at the most recent visit up to the particular time-point.

Data are medians (first quartile, third quartile) or %. Only subjects at risk at the particular time-point were included; for example, at year 10 there were 1391 active participants without a prior MACE event. The number at risk beyond year 24 declines owing to staggered entry of participants into the DCCT during 1983-1989, only 40 being at risk of MACE in year 30.

SUPPLEMENTARY DATA

Supplementary Table 5. The final time-dependent multivariable Cox model for any CVD fit among males.

	Hazard Ratio	95% CI		Z-test value	p-value
Age (per 5 yrs)	1.4831	1.2502	1.7594	4.5222	0
Family History of MI	1.3025	0.8641	1.9632	1.2626	0.2067
Mean systolic BP (per 10 mm Hg)	1.1128	0.8594	1.441	0.8110	0.4173
Mean Pulse (per 10 bpm)	1.5725	1.1519	2.1467	2.8510	0.0043
(Log) Triglycerides	1.6978	1.1748	2.4537	2.8176	0.0048
Mean LDL (per 10 mg/dl)	1.0624	0.9715	1.1619	1.3276	0.1842
Current use of ACE Inhibitor	0.7393	0.4645	1.1767	-1.2735	0.2028
Duration of Diabetes (per 5yrs)	1.2465	0.9817	1.5828	1.8087	0.0704
Mean HbA1c	1.2284	1.0139	1.4883	2.1013	0.0356

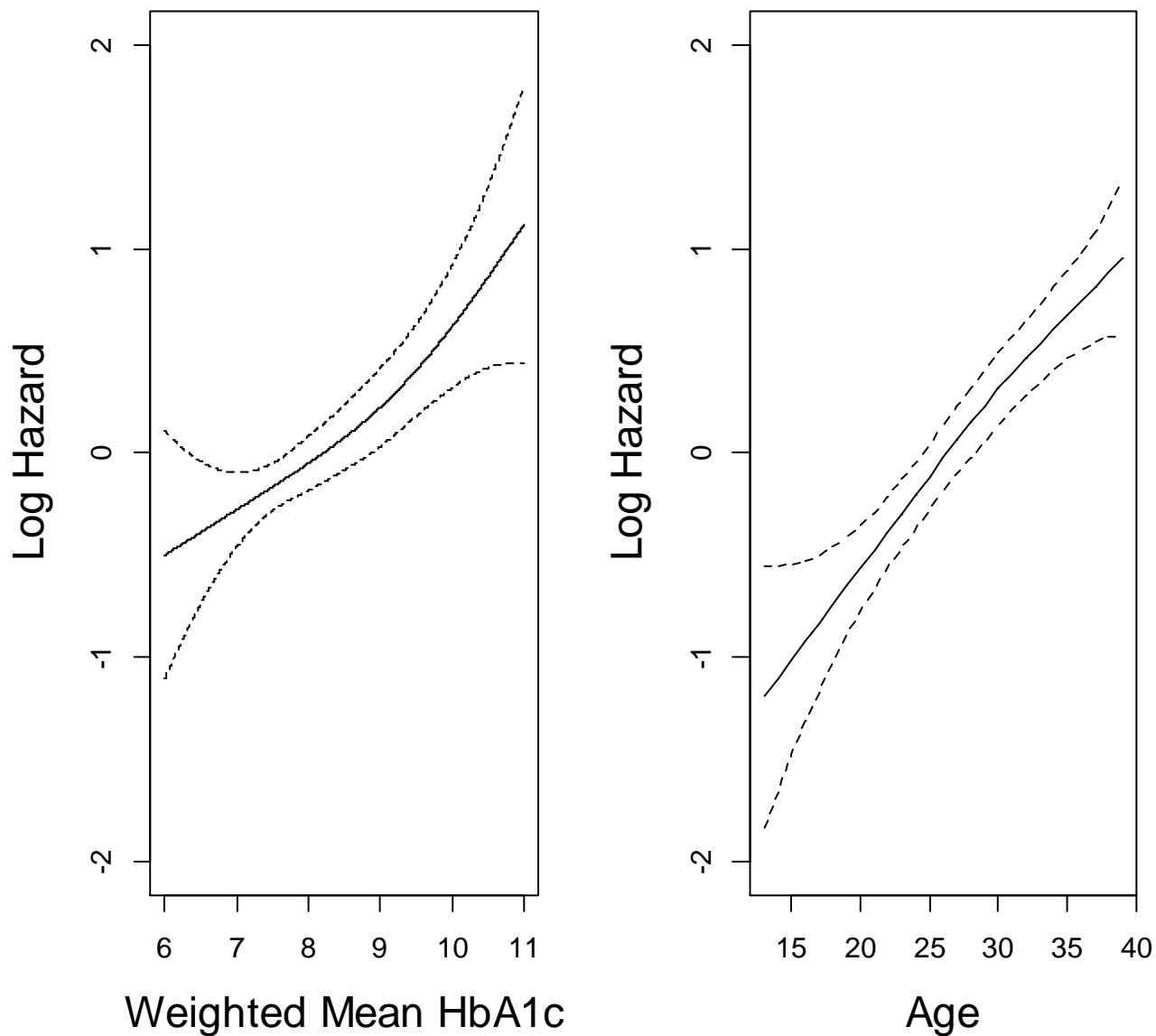
Supplementary Table 6. The final time-dependent multivariable Cox model for any CVD fit among females.

	Hazard Ratio	95% CI		Z-test value	p-value
Age (per 5 yrs)	1.4991	1.2634	1.7786	4.6407	0
Family History of MI	1.4173	0.9127	2.2008	1.5534	0.1203
Mean systolic BP (per 10 mm Hg)	1.6630	1.2819	2.1575	3.8301	0.0001
Mean Pulse (per 10 bpm)	1.1208	0.7694	1.6325	0.5944	0.5522
(Log) Triglycerides	1.3258	0.8362	2.1021	1.1995	0.2303
Mean LDL (per 10 mg/dl)	1.0963	0.993	1.2103	1.8215	0.0685
Current use of ACE Inhibitor	0.5884	0.3495	0.9906	-1.9955	0.0459
Duration of Diabetes (per 5yrs)	1.2388	0.9643	1.5914	1.6757	0.0937
Mean HbA1c	1.4152	1.1780	1.7002	3.7112	0.0002

SUPPLEMENTARY DATA

Supplementary Figure 1. Risk gradients showing the linearity of the log hazard rate for any CVD (A) and for MACE (B) as a function of the weighted mean HbA1c (a time-dependent covariate) and age at baseline.

A. Any CVD



SUPPLEMENTARY DATA

B. MACE

