

ESM Table 1 Registration characteristics in this cohort and entire trial population in ADVANCE study.

Characteristic	Entire trial population in ADVANCE study (n=11,140)	Included participants in this cohort (n=8,879)
Age (years; mean [SD])	65.8 (6.4)	65.6 (6.3)
Men (n [%])	6405 (58)	5108 (58)
Residence in Asia (n [%])	4136 (37)	3523 (40)
Duration of diabetes (years; mean [SD])	7.9 (6.4)	7.8 (6.3)
History of macrovascular disease (n [%])	3590 (32)	2742 (31)
Current treated hypertension (n [%])	7655 (69)	6050 (68)
Current smoking (n [%])	1550 (14)	1224 (14)
Current alcohol drinking (n [%])	3396 (30)	2638 (30)
UACR ($\mu\text{g}/\text{mg}$; median [IQR])	15 (7–40)	14 (7–38)
eGFR ($\text{ml min}^{-1} [1.73 \text{ m}]^{-2}$; mean [SD])	74 (18)	75 (17)
Systolic BP (mmHg; mean [SD])	145 (22)	145 (21)
Diastolic BP (mmHg; mean [SD])	81 (11)	81 (11)
HbA _{1c} (mmol/mol; mean [SD])	59 (18)	58 (16)
HbA _{1c} (%; mean [SD])	7.5 (1.6)	7.5 (1.5)
HDL cholesterol (mmol/L; mean [SD])	1.3 (0.4)	1.3 (0.3)
LDL cholesterol (mmol/L; mean [SD])	3.1 (1.0)	3.1 (1.0)
Triacylglycerol (mmol/L; median [IQR])	1.6 (1.2–2.3)	2.0 (1.2–2.3)
BMI (kg/m^2 ; mean [SD])	28.3 (5.2)	28.2 (5.2)
Randomised BP lowering treatment (n [%])	5569 (50)	4438 (50)
Randomised intensive blood glucose control (n [%])	5571 (50)	4486 (51)

Asia includes China, India, Malaysia and the Philippines.

ESM Table 2 Multivariable analyses of risk factors associated with eGFR slopes over the 20-month eGFR slope ascertainment period according to subgroup at registration

Risk factor		N	eGFR slopes (ml min ⁻¹ [1.73 m] ⁻² year ⁻¹ ; mean [95% CI])	Difference (95% CI)	p	p for trend
Age (years)	55–64	3690	-0.10 (-0.38, 0.18)	Reference		
	65–74	4459	-0.94 (-1.19, -0.68)	-0.83 (-1.22, -0.45)	<0.001	<0.001
	≥75	730	-1.53 (-2.16, -0.91)	-1.43 (-2.13, -0.73)	<0.001	
Sex	Men	5108	-0.60 (-0.84, -0.37)	Reference		
	Women	3771	-0.68 (-0.96, -0.41)	-0.08 (-0.45, 0.29)	0.67	
History of macrovascular disease	No	6137	-0.52 (-0.73, -0.31)	Reference		
	Yes	2742	-0.90 (-1.22, -0.58)	-0.38 (-0.77, 0.00)	0.05	
UACR (µg/mg)	<30	6249	-0.41 (-0.62, -0.20)	Reference	0.05	
	30–300	2318	-0.93 (-1.28, -0.59)	-0.52 (-0.93, -0.12)	0.01	<0.001
	>300	312	-3.09 (-4.04, -2.15)	-2.70 (-3.67, -1.74)	<0.001	
eGFR (ml min ⁻¹ [1.73 m] ⁻²)	≥90	2037	-2.20 (-2.58, -1.82)	Reference		
	60–89	5010	-0.43 (-0.66, -0.19)	1.77 (1.32, 2.22)	<0.001	<0.001
	<60	1832	0.53 (0.13, 0.92)	2.73 (2.16, 3.29)	<0.001	
Systolic BP (mmHg)	<140	3794	-0.55 (-0.82, -0.28)	Reference		
	≥140	5086	-0.70 (-0.94, -0.47)	-0.15 (-0.51, 0.21)	0.40	
HbA _{1c} (mmol/mol [%])	<53 (< 7.0)	3778	-0.11 (-0.37, 0.16)	Reference		
	53-63 (7.0–7.9)	2509	-0.76 (-1.09, -0.44)	-0.66 (-1.08, -0.23)	0.002	<0.001
	≥64 (≥ 8.0)	2425	-1.34 (-1.67, -1.00)	-1.23 (-1.66, -0.80)	<0.001	
HDL cholesterol (mmol/L)	≥1.0	7096	-0.54 (-0.73, -0.34)	Reference		
	<1.0	1783	-1.04 (-1.44, -0.64)	-0.50 (-0.95, -0.05)	0.03	
LDL cholesterol (mmol/L)	<2.6	3025	-0.72 (-1.03, -0.42)	Reference		
	≥2.6	5854	-0.59 (-0.81, -0.37)	0.12 (-0.26, 0.50)	0.53	
BMI (kg/m ²)	<30	6137	-0.58 (-0.79, -0.37)	Reference		
	≥30	2742	-0.76 (-1.08, -0.45)	-0.18 (-0.57, 0.20)	0.35	

ESM Table 3 Adjusted HRs and 95% CIs for study outcomes associated with eGFR slopes over the 20-month eGFR slope ascertainment period

Clinical outcome	eGFR slopes (ml min ⁻¹ [1.73 m] ⁻² year ⁻¹)							p for linear trend	p for quadratic effect
	-5	-4	-3	-2	-1	0	1		
Combined major renal events, macrovascular events and all-cause mortality	1.57 (1.30, 1.90)	1.49 (1.29, 1.72)	1.37 (1.20, 1.56)	1.19 (1.09, 1.31)	1.06 (0.99, 1.12)	1.00 (Reference)	0.98 (0.91, 1.05)	<0.001	0.18
Major renal events	16.70 (8.57, 30.15)	11.09 (6.26, 19.65)	6.14 (3.60, 10.49)	2.65 (1.71, 4.10)	1.30 (0.91, 1.85)	1.00 (Reference)	0.90 (0.62, 1.29)	<0.001	0.48
Major macrovascular events	1.30 (1.02, 1.64)	1.28 (1.07, 1.54)	1.25 (1.06, 1.48)	1.19 (1.06, 1.33)	1.10 (1.02, 1.20)	1.00 (Reference)	0.93 (0.85, 1.02)	0.001	0.80
All-cause mortality	2.11 (1.68, 2.64)	1.85 (1.55, 2.21)	1.54 (1.31, 1.81)	1.20 (1.07, 1.34)	1.00 (0.92, 1.08)	1.00 (Reference)	1.05 (0.96, 1.15)	<0.001	0.005

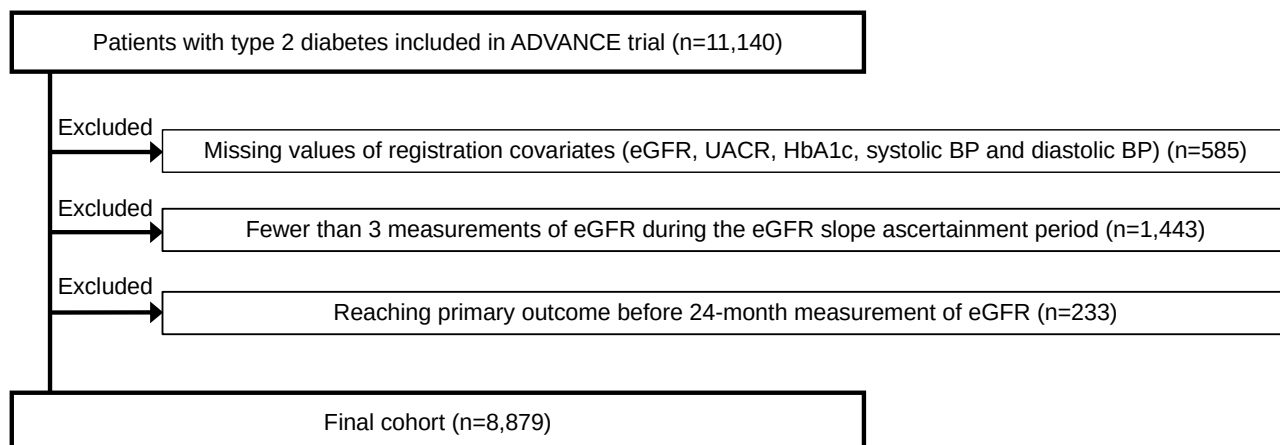
Covariates: registration values of age, sex, region of residence, duration of diabetes, log-transformed UACR, systolic BP, diastolic BP, a history of macrovascular disease, smoking, drinking, treated hypertension, HbA_{1c}, HDL-cholesterol, LDL-cholesterol, log-transformed triacylglycerol and BMI, 4-month eGFR and randomised treatment allocation (BP and glucose treatment)

ESM Table 4 Discrimination statistics for predicting study outcomes in the models including eGFR slope or percent change in eGFR in addition to covariates

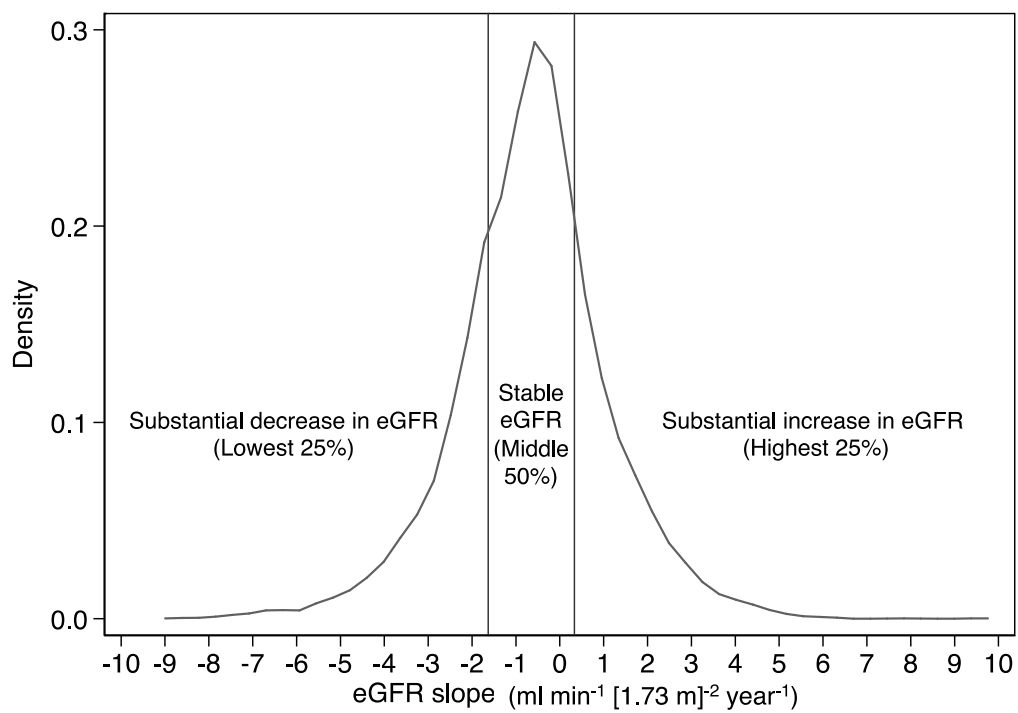
Clinical outcome	Model	AIC	BIC	c-statistic (95% CI)	p
Combined major renal events, macrovascular events and all-cause mortality	eGFR slope	30909.68	31051.26	0.6636 (0.6516, 0.6755)	0.51
	Percent change in eGFR	30911.11	31052.69	0.6633 (0.6514, 0.6752)	
Major renal events	eGFR slope	1401.83	1543.41	0.8679 (0.8322, 0.9035)	0.22
	Percent change in eGFR	1394.66	1536.24	0.8721 (0.8385, 0.9058)	
Major macrovascular events	eGFR slope	19720.89	19862.47	0.6594 (0.6443, 0.6744)	0.41
	Percent change in eGFR	19723.66	19865.25	0.6590 (0.6439, 0.6741)	
All-cause mortality	eGFR slope	19715.13	19856.71	0.7132 (0.6993, 0.7271)	0.93
	Percent change in eGFR	19715.98	19857.56	0.7132 (0.6993, 0.7270)	

Covariates: registration values of age, sex, region of residence, duration of diabetes, log-transformed UACR, systolic BP, diastolic BP, a history of macrovascular disease, smoking, drinking, treated hypertension, HbA_{1c}, HDL-cholesterol, LDL-cholesterol, log-transformed triacylglycerol and BMI, 4-month eGFR and randomised treatment allocation (BP and glucose treatment) AIC, Akaike's information criterion; BIC, Schwarz's Bayesian information criterion.

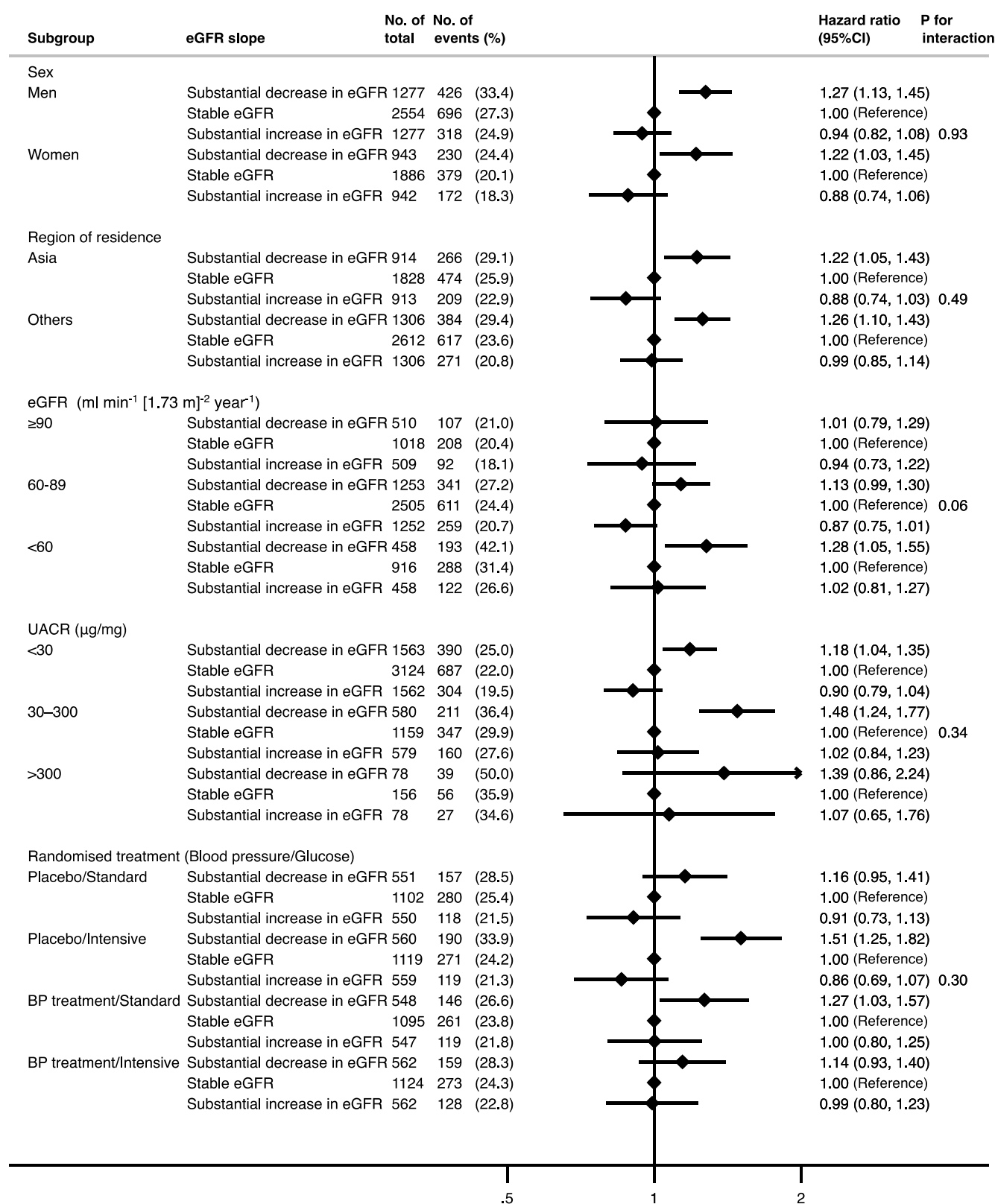
ESM Fig. 1 The identification of study cohort.



ESM Fig. 2 Distribution of eGFR slopes over the 20-month eGFR slope ascertainment period

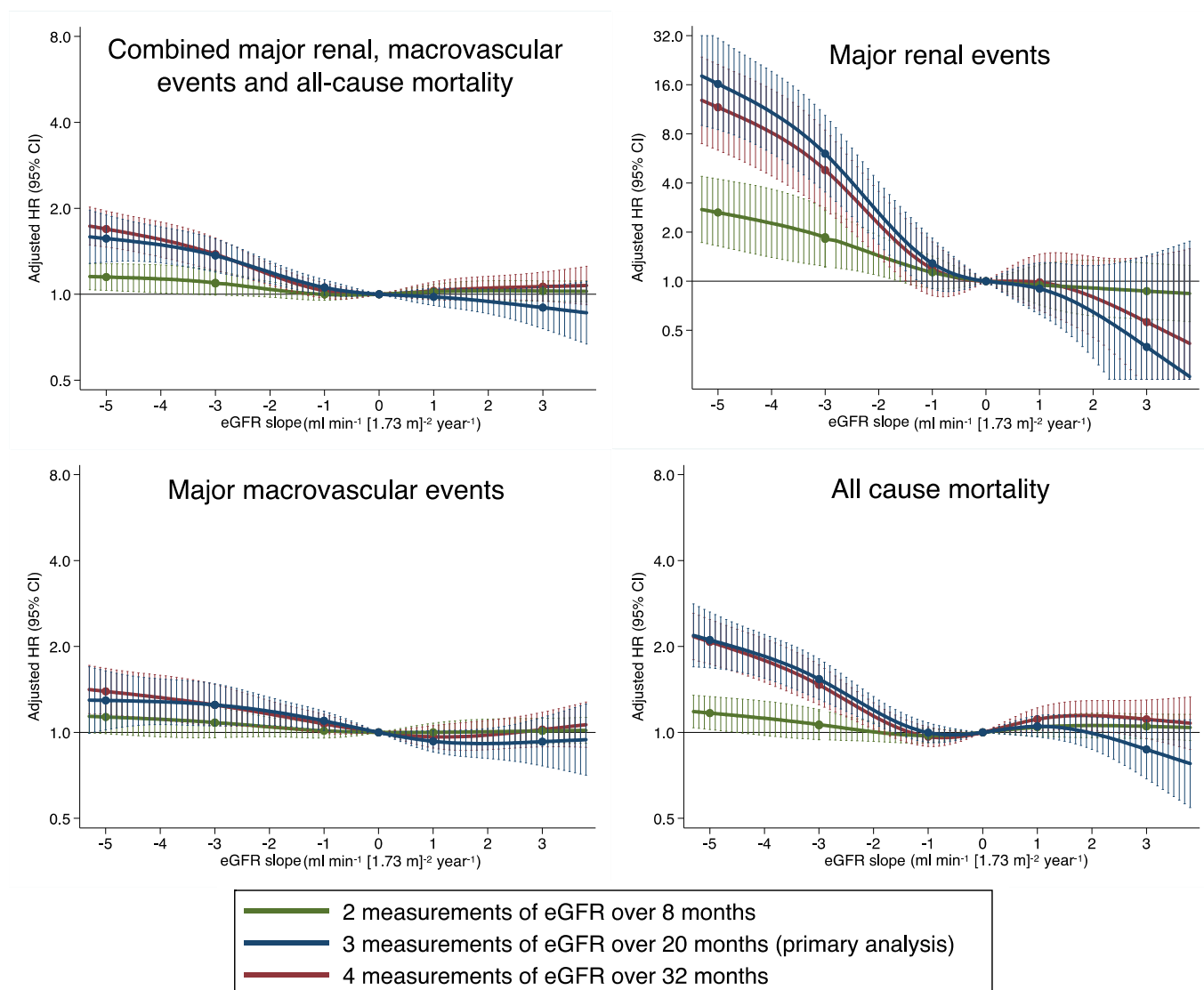


ESM Fig. 3 Adjusted HRs for the composite of major renal events, macrovascular events and all-cause mortality according to categories of eGFR slopes over the 20-month eGFR slope ascertainment period by subgroup at registration



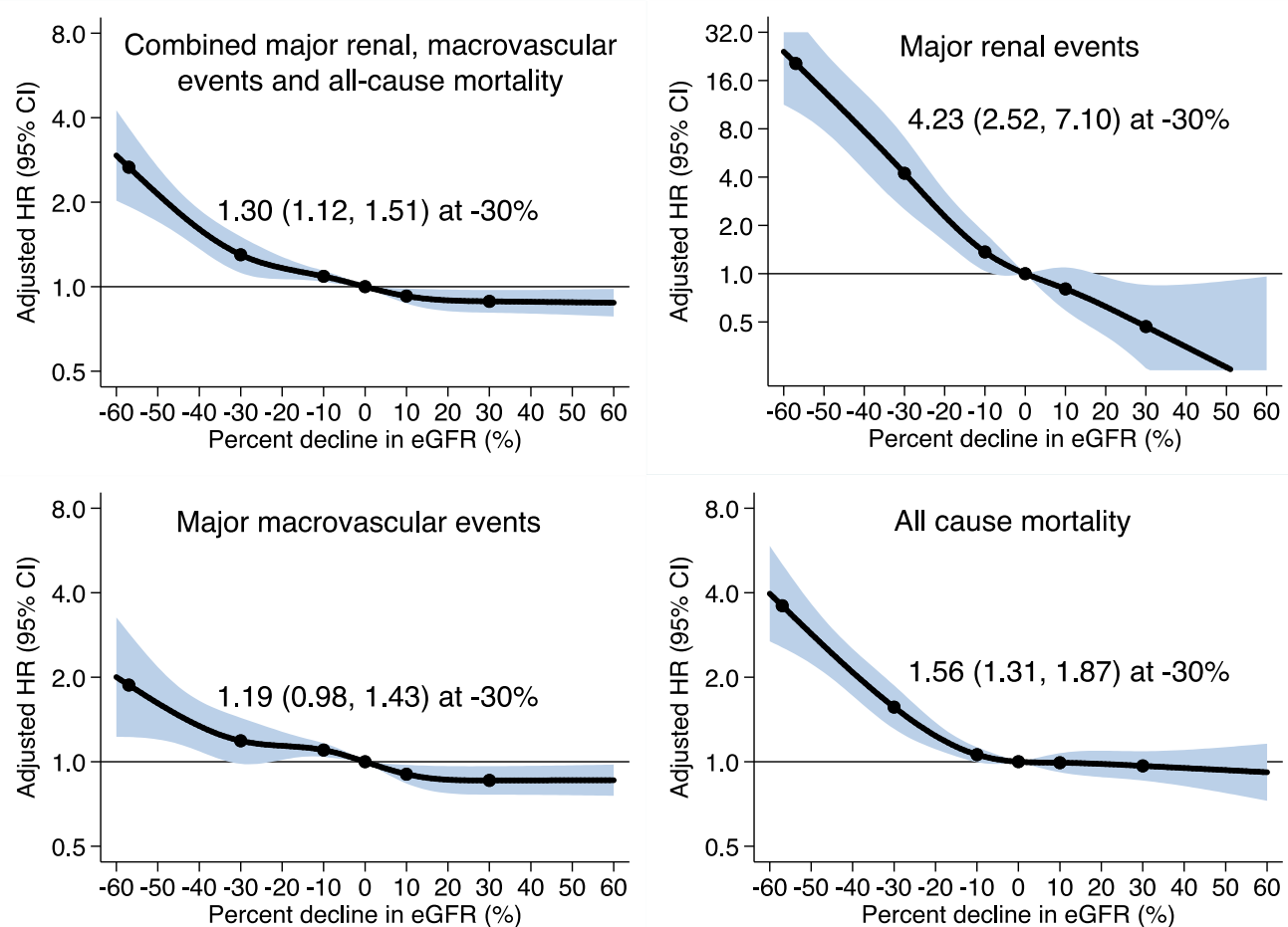
Covariates: registration values of age, sex, region of residence, duration of diabetes, log-transformed UACR, systolic BP, diastolic BP, a history of macrovascular disease, smoking, drinking, treated hypertension, HbA_{1c}, HDL-cholesterol, LDL-cholesterol, log-transformed triacylglycerol and BMI, 4-month eGFR and randomised treatment allocation (BP and glucose treatment)

ESM Fig. 4 Sensitivity analysis: Spline curves showing adjusted HRs and 95% CIs (shaded) for study outcomes associated with eGFR slopes over the 8-, 20- or 32-month eGFR slope ascertainment period



Values were trimmed at a slope of <-5.4 and >3.8 ml min⁻¹ (1.73 m)⁻² year⁻¹. Knots were placed at -5, -3, -1, 1 and 3 ml min⁻¹ (1.73 m)⁻² year⁻¹, using 0 ml min⁻¹ (1.73 m)⁻² year⁻¹ as the reference point. Covariates: registration values of age, sex, region of residence, duration of diabetes, log-transformed UACR, systolic BP, diastolic BP, a history of macrovascular disease, smoking, drinking, treated hypertension, HbA_{1c}, HDL-cholesterol, LDL-cholesterol, log-transformed triacylglycerol and BMI, 4-month eGFR and randomised treatment allocation (BP and glucose treatment)

ESM Fig. 5 Spline curves showing adjusted HRs and 95% CIs (shaded) for study outcomes associated with percent change in eGFR over 20 months



Values were trimmed at a percent change of <-60% and >60%. Knots were placed at -57, -30, -10, 10 and 30%, using 0% as the reference point. Covariates: registration values of age, sex, region of residence, duration of diabetes, log-transformed UACR, systolic BP, diastolic BP, a history of macrovascular disease, smoking, drinking, treated hypertension, HbA_{1c}, HDL-cholesterol, LDL-cholesterol, log-transformed triacylglycerol and BMI, 4-month eGFR and randomised treatment allocation (BP and glucose treatment)