The relationship between estimated glomerular filtration rate trajectory and all-cause mortality in type 2 diabetes: the Fremantle Diabetes Study

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Abstract

Objective: To investigate the association between estimated GFR (eGFR) and all-cause mortality, including the contribution of temporal eGFR changes, in well-characterised community-based patients with type 2 diabetes.

Design: Longitudinal observational study.

Methods: Participants from the Fremantle Diabetes Study Phase 1 were assessed between 1993 and 1996 and followed until end-December 2012. Cox proportional hazards modelling was used to assess the relationship between baseline eGFR category (Stage 1–5) and all-cause death, and between eGFR trajectories assigned by semiparametric group-based modelling (GBM) and all-cause death in patients with five post-baseline annual eGFR measurements.

Results: In the full cohort (1296 patients; mean $\pm$ s.d. age 64.1 ± 11.3 years, 48.6% males), 738 (56.9%) died during 12.9 ± 6.1 years of follow-up. There was a U-shaped relationship between all-cause death and eGFR category. With Stage 3 ($45\text{--}59\text{ mL/min/1.73 m}^2$) as reference, the strongest association was for $\text{eGFR} \geq 90\text{ mL/min/1.73 m}^2$ (hazard ratio (95% CI) 2.01 (1.52–2.66); $P < 0.001$). GBM identified four linear trajectories ('low', 'medium', 'high', 'high/declining') in 532 patients with serial eGFR measurements. With medium trajectory as reference, eGFR trajectory displaced baseline eGFR category as an independent predictor of death, with low and high/declining trajectories associated with more than double the risk (2.03 (1.30–3.18) and 2.24 (1.31–3.83) respectively, $P \leq 0.003$) and associated median reductions in survival of 6.5 and 8.7 years respectively.

Conclusion: There is a nonlinear relationship between eGFR and death in type 2 diabetes, which is at least partially explained by a sub-group of patients with an initially high but then rapidly declining eGFR.

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Introduction

A recent meta-analysis of the association between renal function and mortality involving a variety of epidemiological and intervention studies has shown a 'U-shaped' relationship between baseline-estimated GFR (eGFR) and subsequent all-cause and cardiovascular death in the general population and in people with diabetes (1). Although differentiation of diabetes type

was not possible, most of the patients with diabetes were probably type 2 (1), but a similar relationship has been found with all-cause mortality in a population-based study of type 1 diabetes (2). The eGFR associated with the best prognosis (the nadir of the U-shaped curve) is around $75\text{ mL/min/1.73 m}^2$ regardless of diabetes status (1, 2). Individuals with an eGFR above this level include

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those with glomerular hyperfiltration (an eGFR ≥ 125 to ≥ 140 mL/min/1.73 m² by isotopic measurement in various studies) (3) which has a debated but likely association with more rapid progression of diabetic nephropathy (4) and which may also be an independent predictor of mortality in the general population (5).

The evidence that eGFR has a U-shaped association with mortality, including diabetes, questions the validity of studies which have assessed the prognostic significance of renal disease in statistical models assuming simple linearity or using categorisation that belies the complexity of the relationship. In addition, there is emerging evidence from general population (6) and diabetes (7, 8) studies that a single eGFR does not identify patients in whom a subsequent relatively rapid decline from baseline also portends an adverse prognosis. This sub-group could explain the U-shaped relationship with death observed in studies utilising only baseline eGFR, since those patients with a relatively high initial eGFR could either progress quickly to renal impairment and death or maintain renal function with an associated favourable outcome.

This hypothesis has not been investigated in the general population or in the specific case of type 2 diabetes. Its evaluation would require longitudinal follow-up of a well-characterised community-based sample with clearly identified outcomes, minimal attrition and an adequate duration of follow-up. In addition to conventional modifiable risk factors for renal disease such as hypertension and glycaemia, the availability of genetic determinants would strengthen such an analysis. In the case of diabetic renal disease, these would include polymorphisms of the *ACE* (9), angiotensin II type 1 receptor (*AT1R*) (10), apolipoprotein E (*APOE*) (11) and methylenetetrahydrofolate reductase (*MTHFR*) (12) genes.

A valid method of assigning individuals to categories of changes in renal function over time would also be essential (6). Temporal changes in variables can be characterised using latent class analysis which identifies distinctive clusters of individual trajectories in a larger sample, with the simplest model of best fit selected statistically (13, 14). This group-based modelling (GBM) approach has been used to differentiate groups of patients by time-related changes in key variables in disease contexts such as public health (15), psychiatry (16) and metabolic disorders (17, 18), and in the categorisation of changes in HbA_{1c} in diabetes (19, 20) including FDS1 (21).

To determine whether, in well-characterised, representative, population-based patients with type 2

diabetes, there is evidence of (i) a U-shaped relationship between baseline eGFR and mortality and (ii) sub-groups of patients defined by GBM in which a relatively rapid fall in eGFR is independently associated with death, we have analysed long-term serial eGFR and mortality data from the Fremantle Diabetes Study Phase 1 (FDS1).

Subjects and methods

Study design, setting, patients and approvals

The FDS1 is a natural history study in a postcode-defined urban community of 120 097 people in the state of Western Australia (WA). The FDS1 protocol was approved by the Fremantle Hospital Human Research Ethics Committee, and all subjects gave written informed consent. Descriptions of recruitment and details of non-recruited patients have been published (22). Of 2258 diabetic patients identified from hospital clinic and inpatient lists, local physician referrals, allied health facilities, pharmacies, opticians, advertising in local media and word of mouth between 1993 and 1996, 1426 (63%) entered the FDS1 of whom 1296 (91%) had type 2 diabetes based on age at diagnosis, history of insulin treatment, adiposity and islet autoantibody status if required (23). Eligible patients who were not recruited were a mean of 1.4 years older than participants, but their sex distribution and the distributions of diabetes types and blood glucose-lowering treatments were similar (22, 23).

The aim of FDS1 was for five annual post-baseline face-to-face assessments, and 532 type 2 patients (41.0%) attended all of these. For these 532 patients, there were only 11 (0.3%) missing eGFR values from the total of 3192 which allowed the most accurate categorisation of eGFR trajectory (see below). This group had a variable period of diagnosed diabetes before FDS1 entry, six standardised assessments including baseline and an average of 10 years further follow-up.

Clinical assessment and laboratory tests

At baseline and annual reviews to November 2001, a detailed multifaceted questionnaire was completed, a physical examination and relevant investigations including electrocardiography were performed, and fasting biochemical tests were carried out in a single nationally accredited laboratory using standardised methods that ensured consistency of measurement over time (22). Diabetes-related data including duration were

Table 1 Characteristics of the type 2 diabetes cohort at study entry by vital status at the end of 2012.

	Deceased	Alive	P-value
Number (%)	738 (56.9)	558 (43.1)	
Age at entry (years)	69.3±8.9	56.9±10.1	<0.001
Sex (% male)	52.8	43.0	<0.001
Ethnic background (%):			<0.001
Anglo-Celt	65.2	56.5	
Southern European	17.1	18.6	
Other European	8.9	7.9	
Asian	1.8	5.6	
Indigenous Australian	1.6	1.3	
Mixed/other	5.4	10.2	
Not fluent in English (%)	16.0	14.3	0.44
Education beyond primary level (%)	70.9	78.1	0.004
Currently married/de facto (%)	60.5	72.4	<0.001
Alcohol (standard drinks/day)	0 (0–0.8)	0 (0–0.7)	0.58
Smoking status (% never/ex/current)	40.8/42.8/16.4	49.8/36.8/13.4	0.005
Any exercise in past 2 weeks (%)	67.4	77.8	<0.001
Age at diagnosis (years)	69.4±8.9	56.9±10.1	<0.001
Duration of diabetes (years)	5.0 (1.9–11.0)	2.4 (0.5–6.0)	<0.001
Diabetes treatment (%):			<0.001
Diet	27.0	38.5	
Oral agents	57.7	53.7	
Insulin±oral agents	15.3	7.8	
HbA _{1c} (%)	7.6 (6.6–9.0)	7.2 (6.2–8.6)	<0.001
HbA _{1c} (mmol/mol)	60 (49–75)	55 (44–70)	<0.001
Fasting glucose (mmol/L)	8.5 (6.9–10.80)	8.3 (6.8–10.7)	0.29
Body mass index (kg/m ²)	29.0±5.1	30.3±5.7	<0.001
Obesity (% by waist circumference)	63.9	65.5	0.56
Systolic blood pressure (mmHg)	157±24	143±21	<0.001
Diastolic blood pressure (mmHg)	81±12	80±10	0.023
On anti-hypertensive medication (%)	59.8	39.2	<0.001
Total serum cholesterol (mmol/L)	5.4±1.1	5.5±1.1	0.10
Serum HDL-cholesterol (mmol/L)	1.07±0.34	1.05±0.30	0.23
Serum triglycerides (mmol/L)	1.9 (1.1–3.3)	1.9 (1.1–3.3)	0.34
On lipid-modifying medication (%)	9.4	12.0	0.14
On aspirin ≥75 mg daily (%)	26.7	15.3	<0.001
Urinary albumin: creatinine (mg/mmol)	4.8 (1.0–22.5)	1.7 (0.6–5.4)	<0.001
eGFR categories (n (%)):			<0.001
≥90 mL/min/1.73 m ²	98 (13.4)	190 (34.4)	
60–89 mL/min/1.73 m ²	381 (52.1)	303 (54.9)	
45–59 mL/min/1.73 m ²	159 (21.8)	54 (9.8)	
30–44 mL/min/1.73 m ²	70 (9.6)	4 (0.7)	
<30 mL/min/1.73 m ²	23 (3.1)	1 (0.2)	
Coronary heart disease (%)	39.2	16.8	<0.001
Cerebrovascular disease (%)	14.6	3.8	<0.001
Peripheral arterial disease (%)	40.1	15.5	<0.001
Peripheral sensory neuropathy (%)	41.7	16.9	<0.001
Retinopathy (%)	21.1	10.4	<0.001
Charlson Comorbidity Index:			<0.001
0	60.4	86.2	
1–2	29.7	12.0	
3+	9.9	1.8	
Schizophrenia (%)	0.7	0	0.07
Anti-psychotic medication use (%)	1.8	0.9	0.23
Genotype			
ACE (%; II/ID/DD)	22.1/48.5/29.4	22.0/50.9/27.1	0.62
ATRI (%; AA/AC/CC)	50.4/40.9/8.6	54.1/35.7/10.2	0.16
APOE (%; 22/23/24/33/34/44)	0.6/13.3/2.2/65.6/16.9/1.6	1.1/9.9/2.5/65.5/20.3/0.8	0.17
MTHFR (%; AA/AV/VV)	42.6/42.9/14.5	44.7/44.7/10.6	0.13

Waist circumference ≥102 cm in men and ≥88 cm in women.

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Table 2 Cox proportional hazards model of independent predictors of all-cause death with age as the time-scale for the full cohort with type 2 diabetes.

	HR (95% CI)	P-value
Male	1.52 (1.29–1.78)	<0.001
Aboriginal	3.11 (1.64–5.91)	0.001
Current smoker	1.98 (1.59–2.47)	<0.001
Body mass index (increase of 1 kg/m ²)	1.03 (1.01–1.04)	0.004
Systolic blood pressure (increase in 10 mmHg)	0.92 (0.88–0.96)	<0.001
Diastolic blood pressure (increase in 5 mmHg)	1.07 (1.03–1.12)	0.002
Log _e (urine albumin:creatinine (mg/mmol))*	1.19 (1.13–1.26)	<0.001
Retinopathy	1.43 (1.17–1.75)	0.001
Ischemic heart disease	1.33 (1.11–1.58)	0.002
Peripheral arterial disease	1.33 (1.12–1.57)	0.001
Charlson Comorbidity Index:		<0.001
0	1.00 (reference)	
1–2	1.30 (1.08–1.57)	0.006
3+	2.36 (1.76–3.16)	<0.001
Schizophrenia	3.46 (1.27–9.43)	0.015
eGFR category:		<0.001
≥90 mL/min/1.73 m ²	2.01 (1.52–2.66)	<0.001
60–89 mL/min/1.73 m ²	1.12 (0.92–1.37)	0.30
45–59 mL/min/1.73 m ²	1.00 (reference)	
30–44 mL/min/1.73 m ²	1.18 (0.87–1.61)	0.58
<30 mL/min/1.73 m ²	1.60 (0.97–2.62)	0.09

*A 2.72-fold increase in urinary albumin:creatinine corresponds to an increase of 1 in ln (urinary albumin:creatinine).

obtained from self-report, with verification of details from attendant relatives, and hospital/primary care records if available. Ethnic background was assessed as Anglo-Celt, Southern European, Other European, Asian, Indigenous Australian or Mixed/Other (22).

Chronic complications of diabetes were identified using standard criteria (22), including peripheral sensory neuropathy (>2/8 on the clinical portion of the Michigan Neuropathy Screening Instrument), retinopathy (any grade on direct/indirect ophthalmoscopy and/or ophthalmologist assessment), nephropathy (urinary albumin:creatinine ratio >3.0 mg/mmol), renal impairment by eGFR determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (24), coronary heart disease (history of/hospitalisation for myocardial infarction, angina and/or revascularisation), cerebrovascular disease (history of/hospitalisation for stroke/transient ischaemic attack) and peripheral arterial disease (ankle:brachial index ≤0.90 (either leg) or diabetes-related amputation).

Hyperfiltration was taken as an eGFR ≥120 mL/min/1.73 m², a threshold used previously in studies of

diabetes (25) and which is consistent with the fact that creatinine-based methods tend to underestimate GFR in the hyperfiltration range (variously defined as GFR ≥125 to ≥140 mL/min/1.73 m² by isotopic measurement) (3). However, an age-adjusted threshold was applied, based on the formula 120 mL/min/1.73 m² – 1.0 mL/min/1.73 m² per year after 40 years of age (26).

Insertion/deletion (I/D) polymorphisms of the *ACE* gene were detected by validated PCR supplemented by restriction typing of PCR products (27). The A1166C polymorphism in *ATRI* was identified using mutagenically separated PCR, with an A-allele-specific forward primer, a C-allele-specific forward primer and a reverse primer, with separation of PCR products on 3% agarose gel (27). *APOE* genotype was determined via PCR amplification and restriction enzyme digestion (28). Three co-dominant *APOE* alleles (ε2, ε3, ε4) encode for three different isoforms (E2, E3, E4) with six genotypes. The C677T (rs1801133), a polymorphism in exon 5 of the *MTHFR* gene resulting in substitution of valine for alanine at position 222, was determined by *HinfI* digestion of the PCR products (29).

Mortality and hospital morbidity data

The WA Data Linkage System (WADLS) includes all hospitalisations in WA since 1970, and all death registrations (30). The WADLS was linked to the FDS1 database to provide mortality data from the beginning of the study until end-December 2012. Each subject's Charlson Comorbidity Index (CCI) (31), excluding diabetes and its complications, was also calculated from WADLS data.

Statistical analysis

The computer packages IBM SPSS Statistics 21 (IBM) and Stata IC 13.1 (StataCorp) were used for statistical analysis. Data are presented as proportions, mean ± s.d., geometric mean (s.d. range) or, in the case of variables which did not conform to a normal or log-normal distribution, median and (inter-quartile range). For independent samples, two-way comparisons for proportions were by Fisher's exact test, for normally distributed variables by Student's *t*-test and for non-normally distributed variables by Mann-Whitney *U*-test. Multiple comparisons for proportions were by Fisher's exact test or chi-squared test, for normally distributed variables by ANOVA and for non-normally distributed variables by Kruskal-Wallis test. For statistically significant trends, pairwise comparisons were

Table 3 Comparison of baseline characteristics in patients with type 2 diabetes and eGFR data availability during 5 years of follow-up and the remaining 764 participants.

	Year 5 eGFR	No Year 5 eGFR	P-value
Number (%)	532 (41.0)	764 (59.0)	
Age at study entry (years)	62.4±9.4	65.2±12.3	<0.001
Male (%)	54.2	44.7	0.001
Ethnic background (%):			0.11
Anglo-Celt	64.8	59.0	
Southern European	16.6	18.8	
Other European	8.3	8.6	
Asian	2.8	3.8	
Indigenous Australian	0.6	2.1	
Mixed/other	7.3	7.6	
Any exercise in past 2 weeks (%)	80.0	66.3	<0.001
Smoking status (%):			0.69
Never	44.6	44.7	
Ex-	41.2	39.5	
Current	14.2	15.8	
Body mass index (kg/m ²)	29.3±5.0	29.7±5.7	0.21
Systolic blood pressure (mmHg)	147±22	153±25	<0.001
Diastolic blood pressure (mmHg)	81±10	80±12	0.63
On blood pressure-lowering medication (%)	46.7	53.9	0.013
On angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist therapy (%)	17.9	24.6	0.004
HbA _{1c} (%)	7.2 (6.3–8.5)	7.6 (6.5–9.1)	<0.001
HbA _{1c} (mmol/mol)	55 (45–69)	60 (48–76)	<0.001
Fasting serum glucose (mmol/L)	8.2 (6.8–10.3)	8.6 (6.9–11.1)	0.047
Age at diagnosis (years)	57.6±10.1	58.1±12.7	0.43
Diabetes duration (years)	3.0 (0.7–7.0)	4.4 (1.2–10.0)	<0.001
Diabetes treatment (%):			<0.001
Diet	34.8	30.0	
Oral agents	57.3	55.1	
Insulin±oral agents	7.9	15.0	
Total serum cholesterol (mmol/L)	5.5±1.0	5.5±1.2	0.72
Serum HDL-cholesterol (mmol/L)	1.06±0.33	1.06±0.32	0.97
Serum triglycerides (mmol/L)	1.9 (1.1–3.3)	1.9 (1.1–3.3)	0.87
On lipid-modifying treatment (%)	13.4	8.0	0.002
On aspirin ≥75 mg daily (%)	22.8	21.1	0.49
Coronary heart disease (%)	25.0	32.7	0.004
Cerebrovascular disease (%)	5.3	13.2	<0.001
Peripheral arterial disease (%)	22.2	34.4	<0.001
Peripheral sensory neuropathy (%)	23.1	36.2	<0.001
Retinopathy (%)	11.6	19.9	<0.001
Urinary albumin:creatinine (mg/mmol)	2.3 (0.6–8.5)	3.8 (0.8–17.9)	<0.001
Estimated glomerular filtration rate (%):			<0.001
≥90 mL/min/1.73 m ²	25.4	20.4	
60–89 mL/min/1.73 m ²	56.6	51.0	
45–59 mL/min/1.73 m ²	14.4	18.1	
30–44 mL/min/1.73 m ²	3.2	7.5	
<30 mL/min/1.73 m ²	0.4	2.9	
Deceased by end-December 2012 (%)	42.9	66.7	<0.001

adjusted for multiple comparisons using the Bonferroni correction.

For analysis of predictors of death in all FDS1 type 2 patients, bivariate baseline associates of all-cause death were first determined. Cox proportional hazards modelling, with age as the time scale and left truncation at study entry (employed due to the presence of covariates

strongly associated with age) (32), was used to determine independent predictors of all-cause death, excluding eGFR, using interactive forward conditional modelling ($P<0.05$ for entry, $P>0.10$ for removal) with all clinically plausible variables at $P<0.20$ in bivariate analyses considered for entry into the model. After adjustment for the most parsimonious model, conventional eGFR

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Table 4 Characteristics of FDS1 participants with type 2 diabetes at the Year 5 assessment by eGFR trajectory group.

	Low eGFR	Medium eGFR	High eGFR	High/declining eGFR	P-value
Number (%)	39 (7.3)	188 (35.3)	256 (48.1)	49 (9.2)	
Age (years)	71.0±8.2	68.5±9.3	67.6±9.6 [†]	63.9±8.4**	0.002
Male (%)	46.2	45.2	61.3 ^{††}	57.1	0.006
Duration of diabetes (years)	12.1 (6.9–17.5)	8.4 (6.3–12.0)	8.5 (6.2–11.3)	10.6 (6.1–14.5)	0.041
Southern European (%)	12.8	11.7	18.8	22.4	0.12
Any exercise in past 2 weeks (%)	64.1	69.7	75.0	51.0 [†]	0.007
Smoking status (%):					0.55
Never	38.9	47.7	42.0	43.8	
Ex-	47.2	44.3	43.7	41.7	
Current	13.9	8.0	14.3	14.6	
Body mass index (kg/m ²)	29.9±4.4	29.3±5.3	29.1±4.8	31.1±6.1	0.08
5-year average body mass index (kg/m ²)	30.0±4.3	29.3±5.0	29.0±4.7	30.5±6.1	0.19
Systolic blood pressure (mmHg)	156±22	146±25	145±24	142±22	0.054
5-year average systolic blood pressure (mmHg)	154±17	147±18	146±19	147±17	0.11
Diastolic blood pressure (mmHg)	75±11	72±11	73±11	71±12	0.36
5-year average systolic blood pressure (mmHg)	77±8	76±8	76±8	76±8	0.82
On anti-hypertensive treatment (%)	79.5	53.7*	58.2	63.3	0.022
On angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist therapy (%)	66.7	35.6**	36.3***	53.1	<0.001
HbA _{1c} (%)	7.2 (6.7–8.3)	7.4 (6.5–8.0)	7.4 (6.6–8.4)	7.6 (6.6–8.7)	0.12
5-year average HbA _{1c} (%)	7.2 (6.6–8.1)	7.2 (6.5–8.2)	7.3 (6.6–8.1)	7.3 (6.4–8.7)	0.07
HbA _{1c} (mmol/mol)	55 (50–67)	57 (48–64)	57 (49–68)	60 (49–72)	0.12
5-year average HbA _{1c} (mmol/mol)	55 (49–65)	55 (48–66)	56 (49–65)	56 (46–72)	0.07
Fasting serum glucose (mmol/L)	7.9 (6.2–9.1)	8.7 (6.9–10.4)	8.9 (7.4–10.7)	8.7 (6.7–10.4)	0.51
5-year average fasting serum glucose (mmol/L)	8.2 (7.2–10.3)	8.7 (7.4–10.3)	9.1 (7.9–10.6)	9.1 (7.7–11.7)	0.79
Diabetes treatment (%):				[†]	0.045
Diet	15.4	18.1	20.8	20.4	
Oral agents	69.2	64.4	67.5	49.0	
Insulin±oral agents	15.4	17.6	11.8	30.6	
Total serum cholesterol (mmol/L)	5.5±1.2	5.3±1.0	5.1±0.9	5.0±0.9	0.026
5-year average total serum cholesterol (mmol/L)	5.6±1.0	5.5±0.8	5.4±0.8	5.3±0.7	0.023
Serum HDL-cholesterol (mmol/L)	1.09±0.26	1.21±0.28	1.27±0.35**	1.19±0.34	0.006
5-year average serum HDL-cholesterol (mmol/L)	1.03±0.27	1.12±0.26	1.17±0.31*	1.12±0.33	0.028

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Table 4 (Continued).

	Low eGFR	Medium eGFR	High eGFR	High/declining eGFR	P-value
Serum triglycerides (mmol/L)	2.2 (1.3–3.7)	1.7 (1.0–2.8)*	1.6 (0.9–2.8)**	1.7 (1.0–2.8)	0.014
5-year average serum triglycerides (mmol/L)	2.4 (1.6–3.7)	1.9 (1.2–3.1)*	1.8 (1.1–3.0)**	2.0 (1.3–3.2)	0.004
On lipid-modifying treatment (%)	59.0	42.8	43.1	38.8	0.24
On aspirin $\geq$ 75 mg daily (%)	41.0	33.5	33.1	32.7	0.79
Coronary heart disease (%)	56.4	39.4	36.7	36.7	0.14
Cerebrovascular disease (%)	30.8	13.9	10.5*	12.2	0.015
Peripheral arterial disease (%)	43.6	25.1	20.8*	22.9	0.028
Peripheral sensory neuropathy (%)	64.9	53.1	56.2	54.2	0.62
Retinopathy (%)	30.6	27.5	26.0	36.4	0.53
Urinary albumin:creatinine ratio (ACR) (mg/mmol)	10.8 (2.0–59.2)	2.6 (0.6–11.9)***	2.0 (0.5–8.2)***	4.6 (0.8–25.3)**	<0.001
5-year average ACR (mg/mmol)	10.9 (2.3–50.4)	2.7 (0.7–10.0)***	2.5 (0.7–9.1)***	6.0 (1.1–32.9)††,†††	<0.001
Genotype					
ACE (%; II/ID/DD)	21.6/56.8/21.6	25.5/48.9/25.5	20.3/50.6/29.1	24.5/51.0/24.5	0.83
ATRI (%; AA/AC/CC)	54.1/27.0/18.9	50.5/36.4/13.0	56.4/35.6/13.0	42.9/46.9/10.2	0.17
APOE (%; 22/23/24/33/34/44)	0/18.9/2.7/67.6/10.8/0	0.5/8.2/2.2/71.6/16.9/0.5	0.8/11.6/2.0/70.1/15.5/0	2.0/16.3/4.1/53.1/24.5/0	0.57
MTHFR (%; AA/AV/VV)	40.5/54.1/5.4	45.7/44.0/10.3	41.2/45.6/13.2	40.8/44.9/14.3	0.73
Deceased by 31 December 2012 (%)	71.8	38.3***	42.6**	38.8*	0.002

The 5-year average was calculated for each variable as the mean of all six annual values. For statistically significant trends ($P < 0.05$), * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs lower eGFR trajectory group; † $P < 0.05$, †† $P < 0.01$ vs medium eGFR trajectory group; ††† $P < 0.001$ vs higher eGFR trajectory group, adjusted for multiple pairwise comparisons using the Bonferroni correction.

categories (Stages 1 through 5, or ≥ 90 , 60–89, 45–59, 30–44 and < 30 mL/min/1.73 m²) were entered.

To categorise temporal changes in eGFR during follow-up, GBM was used to identify sub-groups based on heterogeneous longitudinal polynomial eGFR trajectories, an approach we have used previously for HbA_{1c} (21). This was implemented using the procedure ‘traj’ in Stata/IC 13.1 (StataCorp) (14). The censored normal model was used, with uncensored cases handled by specifying a minimum and maximum outside the range of the observed data values (33). The number of groups and degree of polynomial in each trajectory group was determined using the Bayesian Information Criterion, which measures improvement in model fit gained by adding additional groups or shape parameters incorporating a penalty for added complexity (13, 14, 34). Solutions that included small trajectory groups ($< 5\%$ of the sample) were rejected. To assess model fit, the mean posterior probability of group membership was examined (> 0.70 is conventionally recommended).

Cox proportional hazards modelling, with age as the time scale and left truncation at study entry, was used to determine independent predictors of all-cause death in the sub-group with eGFR trajectories using the same strategy as the total sample (developing the most parsimonious model, excluding eGFR and then adding conventional eGFR categories and trajectories to see which, if either, remained in the final adjusted model).

Results

The 1296 FDS1 participants with type 2 diabetes had a mean $\pm$ s.d. age of 64.1 ± 11.3 years, 48.6% were males, and their median (inter-quartile range) diabetes duration was 4.0 (1.0–9.0) years. There were 290 patients (22.4%) with Stage 1 renal impairment based on eGFR, 691 (53.3%) with Stage 2, 216 (16.7%) with Stage 3, 75 (5.8%) with Stage 4 and 24 (1.9%) with Stage 5. Seventy-three patients (5.7%) had baseline hyperfiltration based on age-

Figure 1

Trajectories of eGFR by duration of follow-up in groups of patients with type 2 diabetes from the Fremantle Diabetes Study Phase 1 assuming a linear decline. Mean eGFR values for patients in the low, medium and high trajectories are each shown as $\bullet$ — $\bullet$, and a high/declining trajectory as $\blacktriangle$ --- $\blacktriangle$, with SDs as vertical bars.

adjusted criteria. During 12.9 ± 6.1 (range 0–19.7) years of follow-up, 738 patients (56.9%) died.

Determinants of mortality

The characteristics of those who died compared with those who survived are summarised in Table 1. The deceased patients were older, more likely to be male, had diabetes for longer and were more likely to be insulin-treated, had less well-controlled glycaemia and blood pressure, and were more likely to have chronic complications than those who were still alive at the end of follow-up.

The results of Cox proportional hazards modelling are shown in Table 2. The independent predictors of all-cause death were male gender, current smoking, albuminuria, a high CCI, Aboriginality, increased diastolic blood pressure and body mass index (BMI), schizophrenia and chronic complications (retinopathy, ischaemic heart disease and peripheral arterial disease), while systolic blood pressure was inversely associated. When eGFR category was added to the most parsimonious model, there was a U-shaped relationship in hazard ratios (HRs) with

45–59 mL/min/1.73 m² as reference (HR of 1.0), the strongest association (a doubling of risk) being with an eGFR ≥ 90 mL/min/1.73 m² (HR (95% CI) 2.01 (1.52–2.66); $P < 0.001$).

eGFR trajectories and mortality

Consistent with the requirement for the longitudinal subgroup to have survived ≥ 5 years after recruitment, these 532 patients were younger at entry and less likely to be insulin-treated, and they had shorter diabetes duration, a lower HbA_{1c}, fewer vascular complications and a lower mortality during subsequent follow-up than the 764 remaining type 2 FDS1 subjects ($P < 0.004$; Table 3). In an equivalent Cox model to that for the whole cohort with baseline eGFR 45–59 mL/min/1.73 m² as reference, there was a tendency to a U-shaped relationship between baseline eGFR and all-cause death (HR (95% CI) 1.70 (0.86–3.38) for ≥ 90 mL/min/1.73 m², $P = 0.13$; 1.86 (1.01–3.44) for < 30 mL/min/1.73 m², $P = 0.047$).

There were four trajectories of eGFR over time identified by GBM which were close to linear and which have been termed ‘low’, ‘medium’, ‘high’ and ‘high/declining’ (Fig. 1). The mean $\pm$ s.d. probability of eGFR trajectory group membership was 0.91 ± 0.12 for the low trajectory, 0.91 ± 0.13 for the medium trajectory, 0.91 ± 0.14 for the high trajectory, and 0.76 ± 0.17 for the high/declining trajectory. A low trajectory ($n = 39$) comprised a mean eGFR of 46 mL/min/1.73 m² at baseline and an assumed linear decline in eGFR of 1.6 mL/min/1.73 m² per year during follow-up. The medium trajectory ($n = 188$) included patients with mean eGFR of 68 mL/min/1.73 m² at baseline and a decline of 1.6 mL/min/1.73 m² per year. The high trajectory ($n = 256$) started with a mean eGFR of 86 mL/min/1.73 m² at baseline with a decline of 1.8 mL/min/1.73 m² per year. The high/declining group ($n = 49$) started with a mean eGFR of 89 mL/min/1.73 m² at baseline and had a decline of 4.0 mL/min/1.73 m² per year. There were no patients with hyperfiltration at baseline in the low and medium trajectory groups, while 18 (7.0%) and 7 (14.3%) patients in the high and high/declining groups respectively had hyperfiltration on age-adjusted criteria ($P < 0.001$ by Fisher’s exact test).

The characteristics of the patients in the four trajectory groups at the end of the 5-year period during which annual eGFR measurements were performed (and thus the start of mortality ascertainment for Cox modelling) are shown in Table 4. Those with a high/declining eGFR tended to be younger, more sedentary and more likely to be

Figure 2

Kaplan–Meier curves showing proportions of survivors during follow-up after the fifth Fremantle Diabetes Study Phase 1 assessment in groups of patients with type 2 diabetes defined by eGFR trajectory (high ·····, medium ----, low ---, high/declining —). Age is the time scale and censored points are also shown (◆).

insulin-treated than patients with the other three trajectories, but there were no other consistent distinguishing features including therapies for non-glycaemic cardiovascular risk factors and polymorphisms of the *ACE*, *ATRI*, *APOE* and *MTHFR* genes. During follow-up, 228 (42.9%) of the 532 patients died. All-cause mortality varied from 38.3% in the medium trajectory group to 71.8% in the low trajectory group (Table 4).

Table 5 Independent predictors of subsequent all-cause mortality at the fifth annual Fremantle Diabetes Study Phase 1 review by Cox proportional hazards modelling with eGFR trajectories added to the most parsimonious model.

	HR (95% CI)	P-value
Male gender	1.84 (1.38–2.45)	<0.001
Ln (updated mean urine albumin:creatinine (mg/mmol))*	1.20 (1.09–1.32)	<0.001
eGFR trajectories:		0.002
Low	2.03 (1.30–3.18)	0.002
Medium (reference)	1.0	
High	1.25 (0.92–1.71)	0.15
High/declining	2.24 (1.31–3.83)	0.003

*A 2.72-fold increase in updated mean urinary albumin:creatinine corresponds to an increase of 1 in Ln (updated mean urinary albumin:creatinine).

In a Cox model, male gender and albuminuria were both positive independent predictors of death, as was eGFR trajectory, which displaced eGFR category from the most parsimonious model. With medium trajectory as reference (HR=1.0), both low and high/declining trajectories more than doubled the risk of all-cause mortality (HRs 2.03 (1.30–3.18) and 2.24 (1.31–3.83) respectively, $P \leq 0.003$; Table 5). Kaplan–Meier plots by trajectory are shown in Fig. 2. The median differences in survival versus the medium trajectory were –6.5 and –8.7 years for a low or high/declining trajectory respectively.

Causes of death

The most common cause of death was cardiovascular disease (41%) followed by cancer (26%) with no trends by eGFR trajectory group (Fisher's exact test, $P \geq 0.38$). Nearly 5% of deaths were due to renal disease. There was a tendency for this percentage to be higher in the low and high/declining eGFR trajectory groups (11% in both vs 6% in the medium and 2% in the high eGFR trajectory groups; Fisher's exact test, $P=0.064$), but the number of deaths due to renal disease was small ($n=11$).

Discussion

The present data from the full community-based FDS1 cohort confirm the finding from a large meta-analysis that there is a U-shaped relationship between eGFR and subsequent all-cause death in patients with type 2 diabetes (1). We had access to a variety of risk factors for mortality that were not available in the pooled analysis (1), but the nonlinear independent association with eGFR category remained strong after adjustment. In a separate analysis of longitudinal data collected over 5 years from a large FDS1 sub-group, GBM-based classification of patients by eGFR trajectory proved to be a stronger independent predictor of mortality than simple baseline eGFR category. Both low and high/declining trajectories doubled the risk of subsequent all-cause death relative to a medium trajectory after adjustment for other risk factors, with a median loss of >6 years of life. These observations have important clinical implications, suggesting that the identification of patients with a high/declining phenotype should have a high priority in type 2 diabetes management.

The baseline eGFR associated with the best prognosis in the full FDS1 cohort corresponded to Stage 3 renal impairment (45–59 mL/min/1.73 m²). In the recent meta-analysis, the nadir of the U-shaped relationship between

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eGFR and all-cause death was within Stage 2 (75 mL/min/1.73 m²) (1). The most likely explanation for this discrepancy is patient age. In the majority of studies in the meta-analysis in which, like the FDS1, people with diabetes were identified from a general population, the mean age was younger than in the FDS1 (≤ 64 years in 13 of 23 studies) (1) including one from Taiwan which was five times the size of the next largest ($n=25\,515$) and in which the mean patient age was only 56 years (35). Indeed, binary stratification at age 65 years showed that the U-shaped relationship between eGFR and all-cause death was attenuated in the younger age group (1). The lower nadir in this study is thus likely to reflect the age-related decline in eGFR, which is independent of chronic kidney disease.

The poor prognosis associated with a low baseline eGFR seen in this study is well established (36), including diabetes (37), but the association between a high eGFR and death has been recognised only relatively recently. There are several factors that could underlie this latter relationship. The present patients with an eGFR ≥ 90 mL/min/1.73 m² may have had a reduced muscle mass, with a consequently low serum creatinine and high eGFR. Sarcopenia is predictive of death in general population studies (38). An alternative explanation is that the highest eGFR category in FDS1 contained a disproportionately large percentage of patients with hyperfiltration and others may have progressed through this phase before recruitment. In both these cases, there is an increased associated risk of progression to diabetic nephropathy (39) and, if independent associations in the general population apply to diabetes, an increased risk of sub-clinical and overt cardiovascular disease (40, 41) and all-cause death (5).

Support for the latter explanation comes from GBM-defined eGFR trajectories in a large sub-group of FDS1 patients. Along with the low trajectory group in whom a relatively poor prognosis would be expected (37), the other at-risk patients were those with a high/declining trajectory. The patients in this group tended to be relatively young and insulin-treated, factors which would be against reduced muscle mass, while there was a disproportionately high percentage of hyperfiltrators. In addition, back-extrapolation of the relatively high rate of linear eGFR decline suggests that many patients in this group who had an eGFR below the age-adjusted hyperfiltration threshold at FDS1 entry (when the median diabetes duration was around 5 years) would have passed through a period of hyperfiltration before recruitment.

Definitions of rapid renal decline, with an associated high risk of progression to renal failure and other adverse endpoints in population-based studies, have varied from ≥ 2.4 mL/min/1.73 m² per year in patients with a baseline eGFR of ≥ 60 mL/min/1.73 m² (42) to an average of 12 mL/min/1.73 m² per year in a large sample of Taiwanese adults with a mean baseline eGFR of 91.1 mL/min/1.73 m² (43). In analyses of aggregated data and guideline development, a decline of at least 4–5 mL/min/1.73 m² per year has been recommended (36, 44, 45), a rate which is consistent with the average fall in eGFR of 4.0 mL/min/1.73 m² per year in our high/declining sub-group. Patients in this sub-group typically started at a relatively high baseline eGFR (almost 50% were at Stage 1 or ≥ 90 mL/min/1.73 m² and one in seven were hyperfiltrators), but forward extrapolation of the eGFR decline beyond the 5 years of follow-up suggested that most would have progressed to Stage 4 or 5 renal impairment by the time of death.

The novel clinical implications of the present data relate to patients with type 2 diabetes who have relatively good renal function. The mean baseline eGFRs in the high and high/declining trajectory groups in this study were similar and close to 90 mL/min/1.73 m². Since the small minority (16%) of these combined groups who are in the high risk high/declining trajectory cannot be readily identified by a range of anthropometric, clinical, laboratory and genetic characteristics, it is important that regular eGFR measurements are performed. Given that the rate of eGFR decline is 2–3 times that of the other three trajectory groups, annual assessments should identify high/declining patients within a few years and afford the opportunity to intensify therapy aimed at optimising control of glycaemia and non-glycaemic cardiovascular risk factors. It is of relevance that only 38.8% of the high/declining group were statin-treated at the end of the 5-year follow-up period, while only just over one-half were taking renin-angiotensin system blocking drugs. Optimisation of lifestyle factors (more half had a BMI >30 kg/m²) as well as pharmacotherapy may improve prognosis in these patients.

There is evidence that the progression of renal disease in individual patients can be variable, including relatively complex nonlinear changes in eGFR with time (6). In this study, GBM assigned individual patients to trajectories based on probability and did not exclude those with unusual temporal variability in eGFR. Since eGFR is sensitive to factors such as body weight change, changes in treatment for diabetes and other diseases, and intercurrent illnesses unrelated to diabetes, contextual

clinical interpretation of patterns in serial eGFR measures remains an important part of case management (46).

This study found that the degree of albuminuria was a predictor of all-cause mortality independent of eGFR categories both in the full FDS1 cohort and in the subset in whom trajectories were determined. This relationship has been found in the general population (1, 47) as well as type 2 diabetes (1, 48, 49), and underscores the benefits of including both eGFR and albuminuria in the recently updated renal disease categorisation (45) as well as highlighting the strong links between albuminuria and endothelial function beyond the kidney (50). The other independent risk factors for all-cause death such as male gender, smoking and prior vascular disease were largely as expected, although the inverse relationship with systolic blood pressure likely reflects the nonlinear association between these two variables described in other studies of type 2 diabetes (51).

This study had limitations. As acknowledged, creatinine-based methods including CKD-EPI tend to underestimate GFR at the high end of the range compared with isotopic measurement (3) and this may have influenced the present analyses, especially in relation to the identification of hyperfiltration. Nevertheless, creatinine-based methods are used widely, including in studies showing a U-shaped relationship between eGFR and death in the general population and in diabetes in particular (1, 2). Because trajectory categorisation required 5 years of eGFR data, the patients included in this part of the present analyses were young and healthy survivors compared with the FDS1 type 2 sample as a whole. Nevertheless, we had near-complete data and these patients were followed for long enough to accrue endpoints from an established data linkage system that were sufficient to support valid multivariate analyses of mortality. In addition, the non-glycaemic determinants of all-cause mortality were all clinically plausible, including albuminuria.

In conclusion, the present longitudinal data from a large representative community-based cohort of patients with type 2 diabetes confirm the U-shaped relationship between eGFR and subsequent all-cause mortality found in a range of other studies (1), albeit in a cohort with a wide range of potential explanatory and confounding variables not available in the meta-analysis. However, the use of GBM facilitated the identification of a subgroup of patients with an initially relatively high eGFR who exhibited a rapid decline in renal function over the next 5 years and who had a substantially increased risk of death compared with the patients with a similar

eGFR at baseline but which remained relatively stable during follow-up. The high/declining group did not have clear differentiating baseline features, but their temporal eGFR profile may be a marker of vulnerability to cardiovascular and other causes of mortality that is not captured by conventional risk factors which were adjusted for in the multivariate models. There is, therefore, the need to monitor eGFR regularly, even in those patients well away from clinically concerning degrees of renal impairment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

All authors reviewed the manuscript and approved the final version for publication. T M E D is the principal investigator of FDS1, conceived the present sub-study and wrote the manuscript. S A P C was responsible for all biochemical analyses. W A D performed all statistical analyses.

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