Estimated glomerular filtration rate, albuminuria and mortality in type 2 diabetes: the Casale Monferrato study

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Abstract

Aims/hypothesis Estimated glomerular filtration rate (eGFR) predicts mortality in non-diabetic populations, but its role in people with type 2 diabetes is unknown. We assessed to what extent a reduction in eGFR in people with type 2 diabetes predicts 11-year all-cause and cardiovascular mortality, independently of AER and other cardiovascular risk factors.

Materials and methods The study population was the population-based cohort (n=1,538; median age 68.9 years) of the Casale Monferrato Study. GFR was estimated by the abbreviated Modification of Diet in Renal Disease Study equation.

Results At baseline, the prevalence of chronic kidney disease (eGFR <60 ml min⁻¹ 1.73 m⁻²) was 34.3% (95% CI 33.0–36.8). There were 670 deaths in 10,708 person-years of observation. Hazard ratios of 1.23 (95% CI 1.03–1.47) for all-cause mortality and 1.18 (95% CI 0.92–1.52) for cardiovascular mortality were observed after adjusting for cardiovascular risk factors and AER. When five levels of eGFR were analysed we found that most risk was conferred by eGFR 15–29 ml min⁻¹ 1.73 m⁻², whereas

no increased risk was evident in people with eGFR values between 30 and 59 ml min⁻¹ 1.73 m⁻². In an analysis stratified by AER categories, a significant increasing trend in risk with decreasing eGFR was evident only in people with macroalbuminuria.

Conclusions/interpretation Our study suggests that in type 2 diabetes macroalbuminuria is the main predictor of mortality, independently of both eGFR and cardiovascular risk factors, whereas eGFR provides no further information in normoalbuminuric people.

Keywords Cohort · Diabetic nephropathy · Epidemiology · Mortality · Survey

Abbreviations

apo	apolipoprotein
eGFR	estimated glomerular filtration rate
HR	hazard rate ratio
MDRD	Modification of Diet in Renal Disease (study)

Introduction

Cardiovascular risk is higher among people with chronic kidney disease than among those with normal renal function, even after adjustment for traditional risk factors [1–7]. This association is probably due to systemic atherosclerosis and reduced renal function acting as a marker rather than a determinant of vascular dysfunction. Early identification of people with reduced renal function would make it possible to target treatment and to prevent progression to end-stage renal disease and cardiovascular complications. Compared with non-diabetic people, those with type 2 diabetes are at increased risk of both renal and

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cardiovascular diseases. Thus, the American Diabetes Association has recommended that serum creatinine should be measured at least annually for the estimation of GFR, regardless of the degree of albuminuria, to identify the stage of chronic kidney disease [8]. Whereas the time-consuming and expensive direct measurement of GFR is difficult to perform, the estimated GFR (eGFR) using the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) study has been suggested as the best validated means for transforming serum creatinine measurements into GFR in adults, using age, sex and ethnicity as surrogates for muscle mass [9, 10]. At present no prospective population-based study has assessed the value of eGFR for predicting survival rates in people with type 2 diabetes. Moreover, it is presently unknown whether knowledge of eGFR provides further information on cardiovascular risk in addition to that provided by the albumin excretion rate (AER).

The Casale Monferrato Study is an ongoing Italian population-based study, which in 1988 identified a cohort of people with diagnosed type 2 diabetes and prospectively assesses the incidence of diabetic nephropathy and the risk of mortality [11–14]. The aims of this study were to assess in an 11-year follow-up the ability of eGFR to predict all-cause and cardiovascular mortality, independently of conventional risk factors and AER.

Subjects and methods

The study comprised 1,565 persons with known type 2 diabetes who were resident in 1988 in the town of Casale Monferrato in north-west Italy (93,477 inhabitants). These individuals were invited to undergo a baseline examination in 1991–1992 to assess the prevalence of micro- and macro-albuminuria and cardiovascular risk factors and were followed up until 31 December 2001 [11–14]. Participants were identified from diabetes clinics, general practitioners, hospital discharge records, prescriptions and records of sales of reagent strips and syringes. A high degree of ascertainment was achieved (80%) [15]. Surveys conducted in Italy showed that the participants were representative of patients with diabetes in the country with regard to age, sex, duration of diabetes, BMI and type of glucose-lowering treatment [16].

As described in detail elsewhere, all patients were interviewed and examined by trained investigators at baseline [11]. All individuals gave informed consent and the study was carried out in accordance with the Declaration of Helsinki. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or treatment with antihypertensive drugs. All laboratory determinations were centralised. Venous blood samples were collected after fasting for determination of creatinine, triacylglycerol, total cholesterol, HDL-cholesterol

(enzymatic colorimetric method after precipitation with Mn^{2+}), apolipoprotein (apo) A1, apoB (turbidimetric method, BM/Hitachi 717; BBR, Tokyo, Japan) and HbA_{1c} (HPLC; Daiichi, Menarini, Japan; laboratory reference range 3.8–5.5%). For the purpose of this study, analysis was performed on 1,539 subjects who had baseline serum creatinine measurements (Jaffe method). We estimated GFR by using the four-component abbreviated equation from the MDRD study (all patients were Europids): $\text{eGFR} = 186 \times (\text{serum creatinine}[\text{mg/dl}])^{-1.154} \times \text{age}^{0.203} (\times 0.742 \text{ if female})$ [9]. The distribution of eGFR was divided into five categories: 15–29, 30–44, 45–59, 60–89 and $\geq 90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. People with $\text{eGFR} < 60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ were defined as having chronic kidney disease.

LDL-cholesterol was calculated from Friedewald's formula for all except 44 people in the cohort who had triacylglycerol values $> 4.48 \text{ mmol/l}$ (400 mg/dl). AER was calculated on the basis of the urinary albumin concentration measured in a single, timed, overnight urine sample collected by the nephelometric method (Behring Nephelometer Analyzer; Behring Institute, Marburg, Germany), after exclusion of urinary tract infection, congestive heart failure and other known causes of non-diabetic renal disease. Smoking was classified into: never; ex-smoker if the patient had stopped smoking at least 1 month before the visit; and smoker. For all patients enrolled, the date of diagnosis was recorded.

During the follow-up period (1991–2001) the participants were examined regularly during routine clinical practice, three or four times per year, either at the diabetes clinic or by general practitioners. The relevant time scale for the analysis was time since diagnosis of diabetes to death or to 31 December 2001, whichever came first, with left truncation for the period of time from onset of diabetes to 1991. Information on deaths was obtained from the demographic files of towns of residence and hospital discharge and autopsy records. Only one patient was lost to follow-up. The underlying causes of death were derived and coded by two of the authors (G. Bruno and F. Merletti) according to the ninth revision of the International Classification of Diseases (ICD). Mortality rates were calculated by dividing the number of deaths that occurred during the study period by the number of person-years of observation.

All continuous variables were categorised into quartiles of their distribution, except for age, which was categorised into 5-year age groups (< 60 , 60–64, 65–69, 70–74, 75–79, > 79). The excess risk of death from cardiovascular disease (ICD-9 codes 390–459) and from all causes was expressed as hazard rate ratios (HRs). Variable-adjusted HRs were calculated by multivariate Cox proportional hazards modelling. Given the time scale, all the models were also adjusted for known duration of diabetes. We tested for linear trends across categorical variables by entering a single ordinal term

into the Cox regression model. The proportional hazard assumptions of explanatory variables were assessed on the basis of Schoenfeld residuals. We tested for the effect of age and AER on eGFR by including interaction terms in the models. The likelihood ratio test was used to assess the significance of variables. The *p* value was two-sided; a *p* value <0.05 was considered to indicate statistical significance. All analyses were performed with Stata (release 8.0; Stata Corporation, College Station, TX, USA).

Results

The prevalence of chronic kidney disease (eGFR <60 ml min⁻¹ 1.73 m⁻²) was 34.3% (95% CI 33.0–36.8), and it was higher in women than in men (45.8%, 95% CI 42.4–49.1 vs 19.5%, 95% CI 16.5–22.7), even after age adjustment (odds ratio 3.10, 95% CI 2.42–3.97). In normo-, micro- and macroalbuminuric people, the prevalence of chronic kidney disease was 29.4% (95% CI 26.2–32.8), 35.8% (95% CI 31.5–40.2) and 44.9% (95% CI 38.8–51.1), respectively. Higher risk in micro- and macroalbuminuric people than in those with normoalbuminuria was confirmed after adjustment for age and sex: the odds ratio was 1.38 (95% CI 1.05–1.81) and 2.04 (95% CI 1.47–2.84), respectively.

The baseline features of the cohort by categories of eGFR are shown in Table 1. Persons in the lowest category of eGFR had the highest mean values of duration of diabetes, systolic and diastolic blood pressure, plasma triacylglycerol, apoB, fibrinogen and uric acid. The proportion of patients who had diabetic nephropathy also increased with decreasing eGFR; no normoalbuminuric person had eGFR <30 ml min⁻¹ 1.73 m⁻².

During the 11-year follow-up, 670 deaths were observed in 10,708 person-years of observation. With regard to people with eGFR ≥60 ml min⁻¹ 1.73 m⁻², those with values <60 ml min⁻¹ 1.73 m⁻² had a twofold higher risk of mortality, and an increasing trend across decreasing eGFR categories was also evident (*p* for trend <0.00001; Table 2). With regard to univariate analysis, adjustment for age markedly reduced the strength of this association. In Cox regression analysis (model 1) the HR for eGFR <60 ml min⁻¹ 1.73 m⁻² decreased from 2.16 to 1.39 for cardiovascular mortality and from 1.92 to 1.32 for all-cause mortality after adjustment for age and sex (Table 3). Similar results were obtained when quartiles of plasma creatinine were analysed.

In the fully adjusted model, we found that chronic kidney disease conferred an increased risk of all-cause mortality of 23% and of cardiovascular mortality of 18%, independently of both cardiovascular risk factors and AER.

Table 1 Characteristics of the people with type 2 diabetes in the Casale Monferrato Study according to eGFR at baseline examination (1991–1992)

	eGFR (ml min ⁻¹ 1.73 m ⁻²)					<i>p</i> value
	≥90 (<i>n</i> =113)	60–89 (<i>n</i> =898)	45–59 (<i>n</i> =400)	30–44 (<i>n</i> =106)	15–29 (<i>n</i> =21)	
Age (years)	59.5±10.5	66.6±10.2	73.5±8.7	76.2±8.6	75.4±8.5	<0.0001
Men (%)	87 (77.0%)	451 (50.2%)	95 (23.8%)	26 (24.5%)	9 (39.1%)	<0.0001
Duration of diabetes (years)	10.0±7.0	10.3±6.6	11.4±7.0	12.9±8.1	14.2±8.8	<0.0001
BMI (kg/m ²)	27.5±4.4	27.3±4.8	27.2±4.5	26.7±4.1	27.2±3.9	0.69
HbA _{1c} (%)	8.3±2.4	8.0±2.3	7.9±2.2	8.3±2.2	8.6±2.2	0.23
Total cholesterol (mmol/l)	5.70±1.33	5.76±1.23	5.92±1.26	5.64±1.35	5.48±1.45	0.08
LDL-cholesterol (mmol/l)	3.59±1.18	3.58±1.06	3.71±1.12	3.37±1.08	3.14±1.27	0.02
HDL-cholesterol (mmol/l)	1.47±0.44	1.43±0.42	1.41±0.41	1.27±0.38	1.07±0.32	<0.0001
Triacylglycerol (mmol/l) ^a	1.32	1.47	1.61	1.90	2.34	<0.0001
ApoA1 (g/l)	1.34±0.41	1.35±0.34	1.36±0.34	1.27±0.32	1.20±0.26	0.05
ApoB (g/l)	1.00±0.40	1.02±0.37	1.09±0.38	1.04±0.37	1.18±0.28	0.002
ApoB/apoA1	0.86±0.10	0.78±0.30	0.83±0.32	0.84±0.29	1.00±0.25	0.001
Fibrinogen (g/l)	3.46±0.84	3.56±0.91	3.74±0.93	3.85±0.88	3.94±0.94	0.0001
Uric acid (mmol/l)	280±83	309±95	339±89	393±107	425±149	<0.0001
Blood pressure (mmHg)						
Systolic	145.3±18.6	153.3±21.3	157.5±21.6	162.1±24.8	156.8±23.3	<0.0001
Diastolic	85.1±9.4	87.3±10.4	88.1±10.2	88.6±11.1	88.7±12.6	<0.0001
Hypertension (%)	80 (70.8%)	741 (83.0%)	352 (89.1%)	95 (92.2%)	20 (90.9%)	<0.0001
CHD (%)	22 (23.7%)	162 (21.4%)	94 (28.8%)	37 (38.5%)	6 (27.3%)	0.002
AER (μg/min)						
<20 (100%)	60 (8.0%)	472 (62.6%)	194 (27.7%)	28 (3.7%)	0	<0.0001
20–200 (100%)	39 (8.1%)	270 (56.1%)	125 (26.0%)	38 (7.9%)	8 (1.9%)	
>200 (100%)	12 (4.6%)	133 (50.6%)	67 (25.5%)	38 (14.5%)	13 (4.9%)	

^a Geometric mean

Table 2 Mortality rates in people with type 2 diabetes in the Casale Monferrato Study according to eGFR and serum creatinine quartiles at baseline examination (1991–1992)

	All-cause mortality			Cardiovascular mortality		
	No. of deaths	Rate per 1000 person-years	HR (95% CI)	No. of deaths	Rate per 1000 person-years	HR (95% CI)
eGFR (ml min ⁻¹ 1.73 m ⁻²)						
≥60 (with chronic kidney disease)	366	48.7	1.00	169	22.5	1.00
<60 (without chronic kidney disease)	304	95.3	1.92 (1.64–2.23)	162	50.7	2.16 (1.74–2.68)
Further classification						
≥90	37	42.5	1.00	17	19.5	1.00
60–89	329	49.5	1.18 (0.84–1.66)	152	22.9	1.18 (0.71–1.95)
45–59	217	85.8	2.01 (1.42–2.86)	111	43.8	2.18 (1.31–3.63)
30–44	66	108.8	2.48 (1.66–3.72)	39	64.3	3.07 (1.73–5.44)
15–29	21	377.14	8.29 (4.82–14.27)	12	213.6	10.10 (4.78–21.4)
<i>p</i> for trend			<0.0001			<0.0001
Serum creatinine (μmol/l)						
<80	175	49.6	1.00	84	23.8	1.00
80–87	63	47.3	0.98 (0.73–1.30)	28	21.0	0.90 (0.59–1.38)
88–103	218	62.1	1.29 (1.05–1.57)	102	29.0	1.24 (0.93–1.65)
>103	214	91.6	1.86 (1.52–2.27)	117	50.1	2.08 (1.57–2.75)
<i>p</i> for trend			<0.0001			<0.0001

However, when five levels of eGFR were included in models rather than two levels, a tendency towards a J-shaped pattern of risk was evident. Indeed, compared with people with eGFR ≥ 90 ml min⁻¹ 1.73 m⁻² (HR 1.0), HR was lower in those with eGFR 60–89 ml min⁻¹ 1.73 m⁻² (HR 0.73, 95% CI 0.51–1.05) and higher in those in the lowest category of eGFR for all-cause mortality (HR 2.36, 95% CI 1.28–4.34). A similar pattern was seen for cardiovascular mortality: the HR was 0.65 (95% CI 0.39–1.11) in the eGFR category 60–89 ml min⁻¹ 1.73 m⁻² and 2.03 (95% CI 0.85–4.85) in the lowest eGFR category. The lowest level of eGFR included only 21 subjects; however, 100% of them died during follow-up, compared with 32.7% among those with eGFR ≥ 90 ml min⁻¹ 1.73 m⁻². In the intermediate eGFR categories, frequencies of death were 36.6, 54.3 and 62.3%, respectively.

As the interaction term between age and eGFR was significant ($p < 0.001$), fully adjusted models were also performed separately in people aged <70 years and in those aged ≥ 70 years at baseline. HRs of all-cause mortality in people with eGFR <60 ml min⁻¹ 1.73 m⁻² were 1.51 (95% CI 1.07–2.13) aged <70 years and 1.09 (95% CI 0.89–1.35) in those aged ≥ 70 years; corresponding values for cardiovascular mortality were 1.46 (95% CI 0.85–2.51) and 1.07 (95% CI 0.80–1.42).

As the interaction term between AER and eGFR was significant ($p = 0.023$), we performed a stratified analysis by AER categories, adjusted for age and sex only, given the low numbers of events in each stratum (Table 4). This analysis showed increasing trend of HRs by decreasing eGFR values in macroalbuminuric people only.

Discussion

Our population-based study provides evidence that in persons with type 2 diabetes the most important predictor of all-cause and cardiovascular mortality is AER, whereas GFR estimated with the MDRD study formula has limited clinical usefulness, its predict ability being mainly due to the effects of age, sex and AER.

Our finding is original, no previous prospective study having examined the relationship between eGFR and mortality in a population-based cohort of people with type 2 diabetes. As people with diabetes have increased risk of cardiovascular disease, diabetologists are interested in the identification of factors allowing them to improve the prediction of the individual risk of their patients. Data derived from cohorts of non-diabetic people showing the relationship between reduced eGFR and increased cardiovascular events have suggested that a similar association could also apply to diabetic people [1–7]. Diabetes, however, is characterised by early abnormalities in renal permeability, leading at first to microalbuminuria, a marker of endothelial dysfunction, and then to overt diabetic nephropathy. Both phases, particularly the latter, are characterised not only by an increased risk of progression to end-stage renal disease, but mainly by a higher cardiovascular risk than in people with normoalbuminuria [12, 13, 17, 18]. It is therefore relevant to assess whether eGFR predicts mortality and if this relation is modified by AER values. Two previous clinic-based studies have assessed the effect on survival of eGFR in diabetic people [19, 20]. The study performed in the Veterans Affairs

Table 3 Hazard ratios (HRs) for mortality in people with type 2 diabetes in the Casale Monferrato study

	Model 1 ^a	Model 2 ^b	Model 3 ^c
All-cause mortality			
eGFR (ml min ⁻¹ 1.73 m ⁻²)			
For every ml min ⁻¹ 1.73 m ⁻²	1.24 (1.12–1.38)	1.16 (1.05–1.29)	1.11 (1.00–1.24)
≥60 (with chronic kidney disease)	1.00	1.00	1.00
<60 (without chronic kidney disease)	1.32 (1.11–1.56)	1.24 (1.05–1.47)	1.23 (1.03–1.47)
Further classification			
≥90	1.00	1.00	1.00
60–89	0.83 (0.58–1.17)	0.78 (0.55–1.11)	0.73 (0.51–1.05)
45–59	1.02 (0.70–1.49)	0.95 (0.65–1.38)	0.93 (0.62–1.37)
30–44	1.10 (0.72–1.68)	0.90 (0.58–1.38)	0.74 (0.47–1.16)
15–29	4.12 (2.36–7.18)	2.79 (1.57–4.94)	2.36 (1.28–4.34)
<i>p</i> value for trend	<0.0001	0.005	0.056
AER			
<20 µg/min	1.00	1.00	1.00
20–200	1.41 (1.18–1.68)	1.37 (1.14–1.64)	1.30 (1.08–1.57)
>200	2.29 (1.88–2.79)	2.12 (1.73–2.60)	1.91 (1.54–2.38)
<i>p</i> value for trend	<0.0001	<0.0001	<0.0001
Serum creatinine (mol/l)			
<80	1.00		
80–87	0.98 (0.73–1.31)		
88–103	1.03 (0.84–1.27)		
>103	1.23 (0.99–1.53)		
<i>p</i> value for trend	0.07		
Cardiovascular mortality			
eGFR (ml min ⁻¹ 1.73 m ⁻²)			
For every ml min ⁻¹ 1.73 m ⁻²	1.32 (1.14–1.53)	1.21 (1.05–1.40)	1.09 (0.93–1.27)
≥60 (with chronic kidney disease)	1.00	1.00	1.00
<60 (without chronic kidney disease)	1.39 (1.10–1.76)	1.29 (1.01–1.64)	1.18 (0.92–1.52)
Further classification			
≥90	1.00	1.00	1.00
60–89	0.77 (0.46–1.29)	0.71 (0.42–1.20)	0.65 (0.39–1.11)
45–59	0.96 (0.55–1.67)	0.86 (0.50–1.50)	0.79 (0.45–1.39)
30–44	1.19 (0.65–2.17)	0.94 (0.51–1.73)	0.67 (0.35–1.27)
15–29	4.64 (2.15–10.01)	2.90 (1.31–6.46)	2.03 (0.85–4.85)
<i>p</i> value for trend	<0.0001	0.01	0.27
AER (µg/min)			
<20		1.00	1.00
20–200	1.18 (0.90–1.54)	1.12 (0.86–1.47)	1.06 (0.80–1.40)
>200	2.73 (2.10–3.57)	2.46 (1.87–3.24)	2.00 (1.48–2.71)
<i>p</i> value for trend	<0.0001	<0.0001	<0.0001
Serum creatinine (mol/l)			
<80	1.00		
80–87	0.94 (0.61–1.45)		
88–103	1.03 (0.76–1.38)		
>103	1.05 (1.08–1.98)		
<i>p</i> value for trend	0.02		

^a Adjusted for age and sex^b Adjusted for age, sex, and AER^c Adjusted for age, sex, AER, hypertension, apoB/apoA1, smoking, HbA_{1c} and fibrinogen

Hospital Service showed increasing mortality rates with decreasing eGFR, but no multivariate analyses were reported, so that the results may have been due merely to the confounding effects of age and associated risk factors

[19]. The second study, performed at the Steno Diabetes Center on 227 macroalbuminuric persons, showed that eGFR <60 ml min⁻¹ 1.73 m⁻² was not a risk factor for all-cause mortality, whereas GFR measured by plasma clear-

Table 4 HRs of all-cause and cardiovascular mortality, adjusted for age and sex and stratified by AER categories, in people with type 2 diabetes in the Casale Monferrato Study

	Normoalbuminuria (<i>n</i> =754)	Microalbuminuria (<i>n</i> =477)	Macroalbuminuria (<i>n</i> =257)
All-cause mortality			
eGFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)			
For every $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$	0.90 (0.73–1.10)	1.14 (0.95–1.35)	1.42 (1.20–1.69)
≥60 (with chronic kidney disease)	1.00	1.00	1.00
<60 (without chronic kidney disease)	0.86 (0.65–1.15)	1.40 (1.05–1.87)	1.79 (1.28–2.50)
Further classification			
≥90	1.00	1.00	1.00
60–89	0.91 (0.53–1.54)	0.55 (0.31–0.98)	0.70 (0.29–1.67)
45–59	0.79 (0.44–1.43)	0.85 (0.46–1.57)	1.12 (0.46–2.77)
30–44	0.75 (0.35–1.61)	0.55 (0.27–1.14)	1.23 (0.48–3.13)
15–29	–	1.96 (0.78–4.94)	3.24 (1.15–9.18)
<i>p</i> value for trend	0.29	0.15	<0.0001
Cardiovascular mortality			
eGFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)			
For every $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$	0.90 (0.67–1.19)	1.20 (0.93–1.57)	1.45 (1.16–1.82)
≥60 (with chronic kidney disease)	1.00	1.00	1.00
<60 (without chronic kidney disease)	0.91 (0.61–1.35)	1.41 (0.91–2.21)	1.81 (1.17–2.82)
Further classification			
≥90	1.00	1.00	1.00
60–89	0.74 (0.35–1.58)	0.50 (0.20–1.25)	0.67 (0.20–2.26)
45–59	0.69 (0.30–1.58)	0.73 (0.28–1.93)	1.08 (0.30–3.80)
30–44	0.63 (0.21–1.83)	0.62 (0.21–1.85)	1.18 (0.32–4.34)
15–29	–	2.32 (0.59–9.09)	3.41 (0.83–14.09)
<i>p</i> value for trend	0.45	0.16	0.001

ance of ^{51}Cr -EDTA was associated with mortality in univariate analysis only [20]. Our analyses, based on more than 10,000 person-years at risk and 670 deaths, expand previous knowledge on this issue, showing that chronic kidney disease, defined as $\text{eGFR} < 60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$, increases both all-cause (by 23%) and cardiovascular (by 16%) mortality, independently of cardiovascular risk factors and AER. This effect is mediated through the effect of macroalbuminuria. Indeed, a significant increasing trend in mortality risk with decreasing eGFR was evident only in macroalbuminuric people. Our findings, therefore, have clinical implications, providing evidence that estimating GFR has no advantage over measuring AER, which is the main independent predictor of 11-year cardiovascular mortality in people with diabetes [13]. As our results are based on eGFR, however, future studies are needed to assess both the usefulness and the feasibility in the clinical setting of measuring rather than estimating GFR to provide better prediction of individual risk.

In our study, the prevalence of chronic kidney disease, defined as $\text{eGFR} < 60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$, was high even in the subgroup of 754 normoalbuminuric people examined, of whom one in three had reduced renal function. This

finding is consistent with other studies, suggesting either the involvement of other causes in the prevalence of kidney disease or a reduction in albuminuria resulting from the use of antihypertensive drugs in people with diabetic nephropathy [19–24]. We found that knowledge of eGFR, however, provided no predictive information on long-term mortality in normoalbuminuric people, because eGFR values that defined chronic kidney disease provided no increased risk with respect to $\text{eGFR} > 60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. Our analyses therefore suggest that the MDRD study equation is not well suited to the purpose of early identification of kidney disease in normoalbuminuric patients [22, 23]. Whereas this finding is due to the low accuracy of eGFR with regard to real GFR in people with diabetes or to their peculiarity with regard to the general population is currently unknown. In micro- and macroalbuminuric persons with diabetes, low accuracy of eGFR compared with GFR measured by the plasma clearance of ^{51}Cr -EDTA has recently been shown [20], whereas data in normoalbuminuric people with diabetes are lacking. Moreover, no long-term follow-up study has assessed the predictive value of eGFR in normoalbuminuric people with diabetes. It is likely that the lack of accuracy of eGFR with regard to measured GFR

has resulted in a downward bias of estimates of risk both in previous studies and in ours [19, 20]. Therefore, consistently with others, our findings further emphasise the need for other methods, allowing greater accuracy in measuring GFR than formulas based on creatinine levels, to be implemented in diabetic populations [9].

The MDRD study equation has not yet been validated in people aged >70 years. Our cohort included mainly elderly people, and thus it is possible that the predictive value of eGFR could be higher in middle-aged people. Elderly people are characterised by a reduced muscle mass, so that eGFR in these persons is often overestimated. This finding probably accounts for our observation of a J-shaped curve describing the increased risk of mortality among people with the highest levels of eGFR, and is consistent with a study conducted on more than 4,000 elderly persons, 716 of whom had diabetes [25].

Limitations of our study should be taken into account. Although our analysis was based on 670 deaths in more than 10,000 person-years of observations, the low number of events in each eGFR stratum reduced the power of our study, leading to wide confidence intervals of the HRs, particularly in normoalbuminuric people. The largest proportion of people with diabetes in our cohort had eGFR $>30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$; thus, our findings refer mainly to these people. We employed the MDRD study equation without recalibration of the serum creatinine assay to the assay used in that laboratory; thus, a systematic error could have been introduced into the calculation of the GFR estimate used in our study. This error would be greater at low serum creatinine values, leading to less precise GFR estimates at higher values ($>60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$), whereas at lower levels of GFR calibration errors would be less likely to have a significant impact on the estimated level of GFR and on the stage of kidney disease [9]. At present, however, no international standard for plasma creatinine measurement is available, so our results reflect common clinical practice [9]. As one overnight urine collection was collected at baseline, misclassification of albuminuria categories might have biased our results downwards. The strengths of the study are the representativeness of the study base with regard to the Italian diabetic population, the high estimated completeness of ascertainment, the centralised assessment of measurements and the recruitment of persons cared for both by general practitioners and diabetes clinics, thus limiting the effect of selection bias on our results. Finally, even if the results of our study suggest a limited clinical usefulness of eGFR in predicting cardiovascular disease in patients with diabetes, eGFR maintains its clinical usefulness, more than creatinine alone, when used for drug selection or for adjusting drug doses.

In conclusion, our population-based study suggests that macroalbuminuria is the main predictor of mortality,

independently of both eGFR and cardiovascular risk factors, whereas eGFR provides no further predictive information in normoalbuminuric people.

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