Nephrol Dial Transplant (2011) 26: 3286–3295
doi: 10.1093/ndt/gfr323
Advance Access publication 15 June 2011

Epidemiology and prognostic significance of chronic kidney disease in the elderly—the Three-City prospective cohort study

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Abstract

Background. Little is known about normal kidney function level and the prognostic significance of low estimated glomerular filtration rate (eGFR) in the elderly.

Methods. We determined age and sex distribution of eGFR with both the Modification of Diet in Renal Disease (MDRD) study and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in 8705 community-dwelling elderly aged $\geq$65 years and studied its relation to 6-year mortality. In a subsample of 1298 subjects examined at 4 years, we assessed annual eGFR decline and clinically relevant markers including microalbuminuria (3–30 mg/mmol creatinine) with diabetes, proteinuria $\geq$50 mg/mmol, haemoglobin $<$11 g/L or resistant hypertension despite three drugs.

Results. Median (interquartile range) MDRD eGFR was 78 (68–89) mL/min/1.73m^2 in men and 74 (65–83) in women;

there were 79 (68–87) and 77 (67–85) for CKD-EPI eGFR, respectively. Prevalence of MDRD eGFR <60 mL/min/1.73m^2 was 13.7% and of CKD-EPI eGFR was 12.9%. After adjustment for several confounders, only those with an eGFR <45 mL/min/1.73m^2 had significantly higher all-cause and cardiovascular mortality than those with an eGFR of 75–89 mL/min/1.73m^2 whatever the equation. In the subsample men and women with an MDRD eGFR of 45–59 mL/min/1.73m^2, 15 and 13% had at least one clinical marker and 15 and 3% had microalbuminuria without diabetes, respectively; these percentages were 41 and 21% and 23 and 10% in men and women with eGFR <45, respectively. Mean MDRD eGFR decline rate was steeper in men than in women, 1.75 versus 1.41 mL/min/1.73m^2/year.

Conclusions. Moderately decreased eGFR is more often associated with clinical markers in men than in women. In both sexes, eGFR <45 mL/min/1.73m^2 is related to poor outcomes. The CKD-EPI and the MDRD equations provide very similar prevalence and long-term risk estimates in this elderly population.

Keywords: chronic kidney disease; elderly; glomerular filtration rate; mortality; proteinuria; anaemia

Introduction

Chronic kidney disease (CKD) as defined by the Kidney Disease Outcome Quality Initiative (K/DOQI) is increasingly recognized as a public health priority and targeted in prevention programmes [1–3]. Routine reporting of estimated glomerular filtration rate (eGFR) has led to the identification of up to nearly half of the elderly as having CKD [4–7] with increased referrals to nephrologists [8, 9]. Because CKD diagnosis in many of these subjects is based only on either microalbuminuria or moderately decreased eGFR (i.e. 30–59 mL/min/1.73m^2), controversy exists about its clinical relevance [10–17], especially given how little is known about normal kidney function level [18, 19] and the epidemiology of CKD in the elderly [20, 21].

More information is needed about the prevalence of clinically significant kidney markers such as clinical proteinuria [22], resistant hypertension [23] or anaemia [24, 25] in the older people [21, 26]. Data on eGFR change over time are also needed to better define rapid decline in this population [27–29]. Moreover, although several studies have shown increased mortality risk with decreasing eGFR [30–34], others suggest that age attenuates these associations [35–39]. Finally, use of a creatinine enzymatic assay and development of new equations improved eGFR assessment, but while the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [40] equation has shown to better categorize middle-aged individuals with respect to long-term outcomes compared with the Modification of Diet in Renal Disease (MDRD) study equation [41], distribution of eGFR values according to one another and risk implications in the oldest are unknown [42].

We therefore determined age- and sex-specific eGFR using both the MDRD and CKD-EPI equations in community-dwelling people aged 65 years and older participating in the Three-City (3C) cohort study and studied their relations to 6-year all-cause and cardiovascular mortality risks. In a subsample, we also assessed eGFR decline at 4 years and CKD markers.

Materials and methods

Study design and participants

The 3C study is a community-based prospective cohort that included non-institutionalized individuals aged 65 years or older randomly selected from the electoral rolls of Bordeaux, Dijon and Montpellier (France) from March 1999 through March 2001. The acceptance rate of 37% yielded a sample of 9294 participants. Details of the study design are reported elsewhere [43]. Here, we studied 8705 participants with baseline serum creatinine and mortality data for 6 years; a subsample of 1298 from Bordeaux was also seen at 4 years to assess eGFR decline and CKD markers (Figure 1).

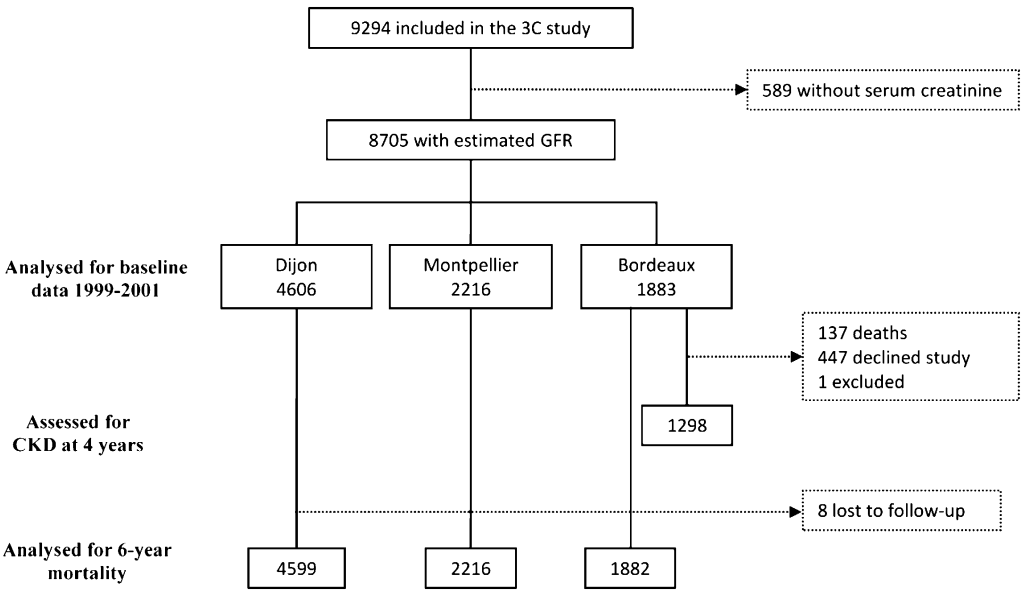

Fig. 1. Three-City study flow chart.

Information

Baseline data came from face-to-face interviews and physical examination. Cardiovascular diseases and cardiorenal risk factors were recorded in detail. Open questions about surgery, hospitalization, treatment and 100% health insurance benefits for severe illness in the last 2 years provided a history of kidney diseases and nephrectomy. At both baseline and 4 years, medication use was recorded and coded according to the World Health Organization's Anatomical Therapeutical Chemical classification [44]; height and weight were measured and body mass index (BMI) was calculated; seated blood pressure (BP) was measured twice after 5-min rest and averaged. Hypertension was defined by a mean systolic BP ≥140 or diastolic BP ≥90 mmHg [45] or by the use of antihypertensive drugs. Resistant hypertension was defined as a mean systolic BP ≥140 or diastolic BP ≥90 mmHg, despite the use of at least three antihypertensive drugs for all participants except those with diabetes or CKD as defined below; thresholds for them were ≥130 or 80 mmHg [23]. Diabetes was either self-reported or defined as fasting glucose ≥7 mmol/L or nonfasting ≥11 mmol/L (in 1% of the participants) or antidiabetic drug treatment. Fasting plasma cholesterol was also measured.

Assessment of kidney function and CKD markers

Serum creatinine was measured with the Jaffe method in a single laboratory at baseline and in a different one at 4 years. In order to standardize creatinine values, 1720 frozen serum samples at baseline and 325 at 4 years were remeasured in a single laboratory with an isotope dilution mass spectrometry (IDMS) traceable enzymatic assay previously shown to provide very reliable eGFR compared to measured GFR [25]. We then developed equations relating the Jaffe and IDMS-traceable creatinine and standardized all baseline (1) and follow-up (2) values as follows: (1) $S_{crIDMS} = 0.86 \times S_{crJaffe} + 4.40$; (2) $S_{crIDMS} = 0.87 \times S_{crJaffe} + 7.85$.

We calculated eGFR in mL/min/1.73m^2 with both the MDRD and the CKD-EPI equations without correction for ethnicity (which was unavailable) [40, 41]. At the 4-year follow-up, blood and urine were collected in 1298 participants and analyzed for haemoglobin (Hb), urinary protein:creatinine ratio (PCR) and albumin:creatinine ratio (ACR) when proteinuria was <300 mg/L. Dipstick haematuria and leukocyturia were recorded. Anaemia was defined as Hb <11 g/dL [24]. Clinical proteinuria was defined as a PCR >50 mg/mmol and microalbuminuria as an ACR of 3–30 mg/mmol. These data were missing for 40 participants. In the subsample at 4 years, we used the UK National Institute for Health and Clinical Excellence (NICE) [22] and 2009 KDIGO Controversies Conference [46] recommended modifications to define CKD Stages 1–2 as a mean eGFR ≥60 mL/min/1.73m^2 with ACR ≥3 mg/mmol or clinical proteinuria; Stage 3A as an eGFR of 45–59 and Stage 3B or higher as eGFR <45.

Mortality

Six-year mortality was assessed by active follow-up of all participants. It remained unknown for only eight participants. Causes of death were ascertained by an adjudication committee using all available medical data from hospitals, family physicians or specialists and proxy interviews as reported earlier [47].

Statistical analysis

We compared baseline characteristics between the participants with and without ($n = 589$) creatinine values, with and without the 4-year follow-up and with and without CKD risk factors—obesity, BP ≥160/100, diabetes, history of cardiovascular disease—or self-reported kidney disease. Subjects without creatinine values were older than those with (76.6 versus 74.2 years), had significantly more cardiovascular diseases but did not differ for other CKD risk factors after adjustment for age (data not shown). We calculated mean, median, interquartile range and 5th percentile for both MDRD and CKD-EPI eGFR, by sex and 5-year age group, in all participants and in those with and without CKD or risk factors. Distribution by eGFR stratum was compared between the two equations. We also provided these values for serum creatinine. Adjusted all-cause and cardiovascular mortality hazard ratios (HRs) associated with MDRD and CKD-EPI eGFR per 15 mL/min/1.73m^2 stratum were then estimated in the overall population and by sex with Cox models and eGFR of 75–89 as the reference category. The eight participants who were lost to follow-up were excluded. Proportional hazard assumption was checked by examining Cox model residuals. An annual eGFR slope in mL/min/1.73m^2/year was calculated for each participant as the difference between baseline and 4-year values divided by exact follow-up time. We used a general linear model to estimate adjusted eGFR slopes (SAS GLM procedure, lsmeans statement with obsmargins option) and 95% confidence intervals, by sex, age, hypertension and diabetes status, and mean eGFR values. The percentages of participants with eGFR decline rate >4 mL/min/1.73m^2 are also shown according to these factors [3]. Finally, we studied the prevalence of each kidney marker according to MDRD eGFR at 4 years. We also evaluated the prevalence of CKD stages at 4 years by sex and diabetes status, as well as the distribution of at least one clinical marker (among microalbuminuria associated with diabetes, clinical proteinuria, resistant hypertension or anaemia), isolated microalbuminuria and low eGFR alone by CKD stage. Statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC) and R 2.8.1 (R Development Core Team, 2009).

Table 1. Baseline characteristics of the 3C study participants[a]

		CKD risk factors or self-reported kidney disease		Subsample with 4-year follow-up
	Overall ($N = 8705$)	No ($N = 3768$)	Yes ($N = 4937$)	($N = 1298$)
Age in years	74.3 ± 5.5	73.3 ± 5.2	75.1 ± 5.7	74.3 ± 4.9
Women	60.5	67.8	54.9	63.5
Income (€ per month)				
<760	5.3	4.7	5.7	8.2
760–1499	28.8	27.5	29.7	35.0
1499–2299	26.8	27.1	26.5	23.0
>2300	33.1	34.5	32.1	28.2
No response	6.0	6.1	6.0	5.6
School education < 9 years	63.1	60.8	64.7	60.2
Smoking				
No	61.2	65.6	57.8	64.8
Yes, past	33.2	28.0	37.3	29.8
Yes, present	5.6	6.4	4.9	5.3
Hypercholesterolaemia				
No	43.4	43.8	43.1	42.4
Yes, not treated	26.5	30.5	23.5	26.1
Yes, treated	30.1	25.8	33.4	31.4
Diabetes[b]	9.7	–	17.1	9.7
Hypertension[c]	77.3	61.3	89.6	77.8
BP ≥ 160/100	26.3	NA	46.4	23.7
BMI > 30 kg/m^2	13.2	NA	23.3	17.4
History of cardiovascular disease	29.6	NA	52.1	29.0
Self-reported kidney disease	0.7	NA	1.3	0.7
Use of renin–angiotensin system inhibitor	22.9	13.9	29.7	22.6
Serum creatinine (μmol/L)	76.4 ± 18.2	73.6 ± 14.4	78.5 ± 20.4	73.8 ± 17.3
MDRD eGFR in mL/min/1.73m^2	76.0 ± 15.6	76.9 ± 14.5	75.2 ± 16.4	78.3 ± 16.3
≥90	16.7	16.9	16.6	20.7
60–89	69.6	73.2	66.8	67.6
30–59	13.4	9.8	16.2	11.4
<30	0.3	0.1	0.4	0.2
CKDEPI eGFR in mL/min/1.73m^2	75.4 ± 13.2	76.9 ± 11.9	74.3 ± 14.0	77.2 ± 12.9
≥90	10.2	11.4	9.3	12.9
60–89	76.9	79.9	74.6	76.9
30–59	12.6	8.6	15.6	9.9
<30	0.3	0.1	0.5	0.4

[a]Values are means ± SD or percent.
[b]Diabetes was either self-reported or defined as fasting glycaemia ≥ 7mmol/L or nonfasting glycaemia ≥ 11 mmol/L or antidiabetic drug treatment.
[c]Hypertension defined as BP ≥140/90 mmHg or antihypertensive drug treatment (stage 2 defined as BP ≥ 160 /100 mmHg with or without antihypertensive drug treatment) [45]. NA, not applicable.

Table 2. Age- and sex-specific eGFR values in mL/min/1.73m^2 calculated with the MDRD and CKD-EPI equations in all participants and by subgroup[a]

		All 3C participants					Participants without CKD risk factors[b] or self-reported kidney disease					Participants with CKD risk factors[b] or self-reported kidney disease				
	Age	*N*	Mean ± Std	Median (minimum–maximum)	P5	Q1–Q3	N	Mean ± SD	Median (minimum–maximum)	P5	Q1–Q3	N	Mean ± SD	Median (minimum–maximum)	P5	Q1–Q3
MDRD eGFR																
All	65–69	2277	79 ± 15	78 (17–168)	58	69–88	1217	79 ± 14	78 (30–168)	58	69–87	1060	79 ± 15	78 (17–132)	57	70–89
	70–74	2808	77 ± 15	77 (25–176)	53	68–86	1248	78 ± 14	77 (30–154)	56	69–86	1560	77 ± 16	77 (25–176)	51	68–86
	75–79	2307	74 ± 15	73 (20–135)	51	64–84	902	75 ± 14	74 (30–132)	53	65–84	1405	74 ± 16	73 (20–135)	49	63–84
	80–84	884	71 ± 17	71 (18–130)	45	61–82	287	74 ± 16	73 (28–120)	51	63–83	597	70 ± 17	69 (18–130)	43	59–82
	85–89	356	68 ± 17	68 (18–121)	40	57–80	97	72 ± 16	71 (37–121)	46	59–82	259	67 ± 17	67 (18–116)	37	56–77
	≥90	73	65 ± 16	66 (26–101)	40	51–76	17	69 ± 14	69 (44–97)	44	60–78	56	64 ± 17	63 (26–101)	39	51–75
	All	8705	76 ± 16	75 (17–176)	51	66–85	3768	77 ± 15	76 (28–168)	54	67–85	4937	75 ± 16	75 (17–176)	49	65–85
Men	65–69	900	83 ± 15	81 (17–137)	60	73–92	399	84 ± 15	82 (44–137)	62	73–93	501	82 ± 16	81 (17–130)	59	72–90
	70–74	1170	80 ± 16	80 (28–154)	53	70–89	416	82 ± 15	81 (45–154)	61	71–89	754	79 ± 16	80 (28–129)	51	69–89
	75–79	857	76 ± 17	75 (20–135)	50	65–87	269	77 ± 15	77 (37–132)	55	68–86	588	75 ± 17	74 (20–135)	48	63–87
	80–84	339	75 ± 18	75 (19–130)	46	62–87	90	79 ± 17	78 (35–120)	50	68–88	249	73 ± 18	73 (19–130)	43	60–87
	85–89	152	70 ± 18	69 (18–116)	41	59–81	34	74 ± 15	72 (48–112)	51	63–82	118	69 ± 19	68 (18–116)	35	57–81
	≥90	23	64 ± 15	63 (41–101)	43	51–73	4	64 ± 5	64 (59–69)	59	60–69	19	64 ± 16	63 (41–101)	41	51–74
	All	3441	78 ± 17	78 (17–154)	51	68–89	1212	81 ± 15	80 (35–154)	57	71–90	2229	77 ± 17	77 (17–135)	49	67–88
Women	65–69	1377	77 ± 14	76 (30–168)	57	68–85	818	76 ± 13	75 (30–168)	57	68–84	559	77 ± 15	76 (31–132)	55	67–87
	70–74	1638	76 ± 14	75 (25–176)	53	67–84	832	76 ± 14	75 (30–125)	54	67–83	806	76 ± 15	76 (25–176)	52	67–84
	75–79	1450	73 ± 14	72 (26–133)	51	64–82	633	74 ± 14	73 (30–123)	53	64–82	817	73 ± 15	72 (26–133)	49	63–82
	80–84	545	70 ± 16	68 (18–122)	44	59–79	197	71 ± 15	71 (28–117)	51	62–81	348	68 ± 16	67 (18–122)	43	58–78
	85–89	204	67 ± 17	67 (27–121)	40	56–79	63	71 ± 17	69 (37–121)	44	57–83	141	66 ± 16	66 (27–106)	38	55–76
	≥90	50	66 ± 17	68 (26–97)	39	51–78	13	71±16	72 (44–97)	44	66–78	37	64±18	64 (26–95)	39	50–76
	All	5264	74 ± 15	74 (18–176)	51	65–83	2556	75 ± 14	74 (28–168)	53	66–83	2708	74 ± 16	73 (18–176)	48	64–83
CKD-EPI eGFR																
All	65–69	2277	80 ± 12	82 (16–109)	60	73–90	1217	81 ± 11	82 (31–109)	61	73–90	1060	80 ± 12	82 (16–101)	59	73–90
	70–74	2808	77 ± 12	80 (25–106)	54	70–87	1248	78 ± 11	80 (30–106)	57	71–87	1560	77 ± 13	80 (25–106)	52	70–87
	75–79	2307	73 ± 12	74 (19–99)	50	65–84	902	74 ± 11	75 (30–97)	53	66–84	1405	72 ± 13	74 (19–99)	48	64–84
	80–84	884	69 ± 14	70 (16–93)	44	60–81	287	71 ± 13	73 (27–92)	49	62–81	597	67 ± 14	69 (16–93)	41	58–80
	85–89	356	64 ± 14	66 (16–89)	38	55–77	97	67 ± 13	68 (35–89)	44	58–79	259	63 ± 15	64 (16–88)	35	53–76
	≥90	73	60 ± 14	62 (24–80)	37	49–73	17	64 ± 11	65 (41–78)	41	56–75	56	59 ± 15	59 (24–80)	36	47–73
	All	8705	75 ± 13	78 (16–109)	51	67–86	3768	77 ± 12	79 (27–109)	55	69–86	4937	74 ± 14	77 (16–106)	47	66–85
Men	65–69	900	82 ± 11	85 (16–106)	61	75–90	399	83 ± 11	86 (45–106)	63	76–91	501	81 ± 12	84 (16–101)	60	75–90
	70–74	1170	78 ± 12	82 (27–106)	53	71–87	416	80 ± 11	83 (45–106)	61	72–87	754	77 ± 13	81 (27–100)	51	70–87
	75–79	857	73 ± 13	75 (19–99)	49	64–84	269	74 ± 12	76 (35–97)	54	67–84	588	72 ± 14	74 (19–99)	47	63–84
	80–84	339	70 ± 14	73 (18–93)	44	60–82	90	73 ± 12	76 (33–92)	48	66–83	249	69 ± 15	71 (18–93)	41	58–81
	85–89	152	65 ± 14	66 (16–88)	38	56–77	34	68 ± 11	68 (45–87)	47	59–78	118	64 ± 15	65 (16–88)	32	54–77
	≥90	23	58 ± 12	59 (36–80)	39	47–69	4	60 ± 5	60 (55–65)	55	55–64	19	58 ± 14	59 (36–80)	36	47–70
	All	3441	76 ± 14	79 (16–106)	50	68–87	1212	79 ± 12	81 (33–106)	56	71–87	2229	75 ± 14	78 (16–101)	47	67–86

Continued

Table 2. *Continued*

	Age	All 3C participants					Participants without CKD risk factors[b] or self-reported kidney disease					Participants with CKD risk factors[b] or self-reported kidney disease				
		N	Mean ± Std	Median (minimum–maximum)	P5	Q1–Q3	N	Mean ± SD	Median (minimum–maximum)	P5	Q1–Q3	N	Mean ± SD	Median (minimum–maximum)	P5	Q1–Q3
Women	65–69	1377	80 ± 11	81 (31–109)	59	72–90	818	79 ± 11	81 (31–109)	60	72–89	559	80 ± 12	81 (32–101)	58	71–90
	70–74	1638	77 ± 12	79 (25–106)	55	70–87	832	77 ± 11	79 (30–98)	56	70–87	806	77 ± 12	79 (25–106)	54	70–87
	75–79	1450	73 ± 12	74 (25–97)	51	65–83	633	73 ± 11	75 (30–94)	53	65–83	817	73 ± 13	74 (25–97)	49	64–84
	80–84	545	68 ± 14	68 (16–92)	44	59–79	197	70 ± 13	72 (27–91)	50	61–81	348	67 ± 14	67 (16–92)	43	58–79
	85–89	204	64 ± 14	65 (25–89)	38	55–77	63	67 ± 14	68 (35–89)	43	55–79	141	63 ± 14	64 (25–84)	35	53–75
	≥90	50	61 ± 15	65 (24–80)	37	49–75	13	65 ± 12	69 (41–78)	41	62–75	37	60 ± 16	61 (24–80)	36	47–74
	All	5264	75 ± 13	77 (16–109)	51	67–85	2556	76 ± 12	77 (27–109)	54	68–86	2708	74 ± 14	76 (16–106)	48	65–85

[a]eGFR, glomerular filtration rate estimated with the MDRD, Modification of Diet in Renal Disease study and the CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration equations; P5, Q1-Q3, are the 5th percentile and interquartile range of the eGFR distribution.
[b]Obesity, BP ≥160/100, diabetes and cardiovascular history.

Table 3. Number of participants (%) reclassified into upper or lower eGFR categories using CKD-EPI versus MDRD study equation[a]

		CKD-EPI eGFR (mL/min/1.73m^2)					
		<30	30–44	45–59	60–89	>90	Total
MDRD eGFR (mL/min/1.73m^2)	<30	25 (0.3)	0 0	0 0	0 0	0 0	25
	30–44	5 (0.1)	171 (2.0)	6 (0.1)	0 0	0 0	182
	45–59	0 0	18 (0.2)	849 (9.8)	117 (1.3)	0 0	984
	60–89	0 0	0 0	49 (0.6)	5,914 (67.9)	93 (1.1)	6056
	>90	0 0	0 0	0 0	663 (7.6)	795 (9.1)	1458
	Total	30	189	904	6694	888	8705

[a]In the upper diagonal, eGFR CKD-EPI underestimates eGFR compared to MDRD study equation, whereas it overestimates into the lower diagonal. eGFR, estimated glomerular filtration rate with the CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration and the MDRD, Modification of Diet in Renal Disease study equations.

Results

Baseline characteristics

More than 80% of the participants had at least one CKD risk factor, but fewer than 1% reported kidney disease (Table 1). They were older, more often men and had lower eGFR with either equation than their counterparts without CKD risk factors or kidney disease (all P-values < 0.0001). Baseline eGFRs and BMI were higher in participants with than without the 4-year follow-up ($P < 0.001$); they were also more often women and had less Stage 2 hypertension ($P < 0.05$), but other characteristics were similar.

Age- and sex-specific serum creatinine and eGFR values

MDRD eGFRs ranged from 17 to 176 mL/min/1.73m^2 and CKD-EPI eGFRs from 16 to 109 mL/min/1.73m^2, for serum creatinine values from 32 to 322 μmol/L (Table 2 and Supplementary Table 1). Gradient for age was steeper with the CKD-EPI than the MDRD equation. Mean eGFR was higher in men than in women using either equation, but differences between sexes were attenuated with the CKD-EPI equation. All eGFR values were lower in participants with than without CKD risk factors. The CKD-EPI equation reclassified 117 participants (9.8%) with MDRD eGFR <60 mL/min/1.73m^2 upward to an eGFR ≥60 and 49 (<1%) with MDRD eGFR ≥60 downward to an eGFR <60; 49.3% of those with MDRD eGFR ≥90 were reclassified downward (Table 3).

HRs for 6-year mortality related to baseline eGFR

After adjustment for several confounders, only those with an eGFR <45 mL/min/1.73m^2 had significantly higher all-cause mortality than those with an eGFR of 75 to 89 mL/min/1.73m^2, in both men and women and with either equation (Table 4). Cardiovascular mortality significantly exceeded that of the reference group for eGFRs <60 mL/min/1.73m^2 in the overall population, but for each sex taken separately, it significantly exceeded only for eGFR <45 mL/min/1.73m^2.

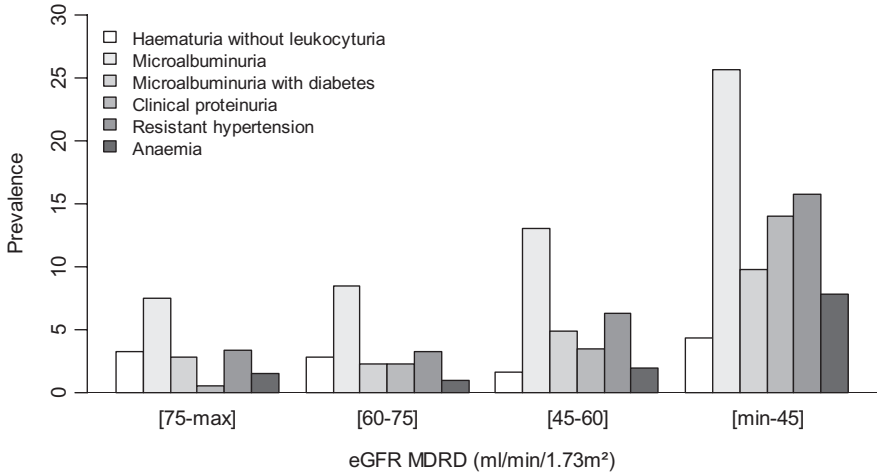

Fig. 2. Prevalence of kidney damage markers according to eGFR level in the subsample microalbuminuria defined as an albumin:creatinine ratio ≥3 (30) and <30 (300) mg/mmol (mg/g) and clinical proteinuria as a protein:creatinine ratio ≥50 mg/mmol (≥500 mg/g). Resistant hypertension defined as a BP ≥130/80 mmHg for those with an eGFR <60 mL/min/1.73m^2, diabetes, proteinuria ≥50 mg/mmol or albuminuria ≥30 mg/mmol, otherwise the threshold was 140/90 mmHg. Anaemia was defined as an haemoglobin <11 g/dL

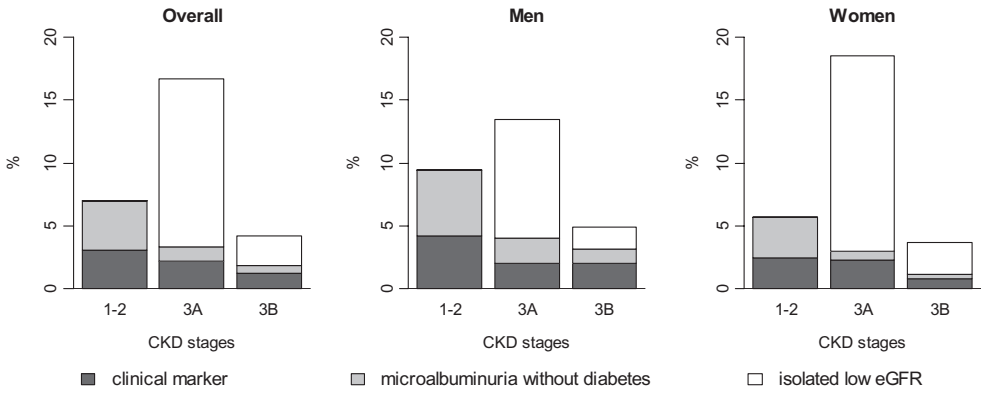

Fig. 3. Prevalence of CKD stages and distribution of isolated low eGFR, microalbuminuria without diabetes and at least one clinically relevant marker by CKD stage and sex microalbuminuria defined as an albumin:creatinine ratio ≥3 (30) and <30 (300) mg/mmol (mg/g); clinically relevant markers include microalbuminuria with diabetes, clinical proteinuria defined as a protein:creatinine ratio ≥50 mg/mmol (≥500 mg/g), anaemia defined as an haemoglobin <11 g/dL and resistant hypertension defined as a BP ≥130/80 mmHg for those with an eGFR <60 mL/min/1.73m^2, diabetes, proteinuria ≥50 mg/mmol or albuminuria ≥30 mg/mmol, otherwise the threshold was 140/90 mmHg.

eGFR decline according to participant baseline characteristics and mean eGFR

In the 1298 participants with a 4-year follow-up, the MDRD eGFR decreased in nearly 4 of 10 by >2 mL/min/1.73m^2/year, 1 of 6 by >4 and in 10% by >5 mL/min/1.73m^2/year (Table 5). The adjusted mean annual decline was significantly steeper in men than in women and in those with than without diabetes at baseline but was not related to age and individual mean MDRD eGFR. There was a nonsignificant trend toward steeper decline with increasing BP in those with hypertension. Mean CKD-EPI eGFR decline was 1.53 ± 2.35 mL/min/1.73m^2/year and was similarly related with studied factors (data not shown).

Prevalence of kidney damage markers according to mean MDRD eGFR level

In the subsample, as MDRD eGFR decreased from ≥75 to <45 mL/min/1.73m^2, the prevalence of microalbuminuria increased from 7.4 to 25.6%, that of microalbuminuria associated with diabetes from 2.8 to 9.8%, clinical proteinuria from 0.6 to 14.0%, resistant hypertension from 3.3 to 15.7% and of anaemia from 1.5 to 7.5% (Figure 2). Haematuria without leukocyturia did not increase with decreasing MDRD eGFR.

Prevalence of CKD stages and percentage of kidney damage markers by stage

In the subsample, the prevalence of CKD using MDRD eGFR was 27.9%; it was 7.0% for Stages 1–2, 16.7% for 3A and 4.2% for 3B or higher (Figure 3). More men than women had CKD Stages 1–2, but more women than men had Stage 3. Nearly half of both men and women at Stages 1–2 had at least one clinically relevant marker and the other half microalbuminuria alone. In men and women with Stage 3A, 30 and 16% had markers of kidney damage, and with Stage 3B or higher, 64 and 31%, respectively. The prevalence of CKD Stages 1–2 was three times higher in those with than without diabetes, 15.7 versus 5.7%; it was closer for other stages: 15.1 versus 16.9% for Stage 3A and 5.7 versus 3.9% for Stage 3B or higher. Using CKD-EPI, the overall

Table 4. Adjusted HRs for 6-year all-cause and cardiovascular mortality related to baseline eGFR using either the MDRD or CKD-EPI equation, overall and by sex[a]

	eGFR in ml/min/1.73m^2					
	≥90	75–89	60–74	45–59	30–44	<30
All participants						
MDRD	1458	3018	3032	982	182	25
CKD-EPI	888	4075	2612	903	189	30
All-cause mortality						
MDRD	1.1 (0.9–1.4)	1 (ref)	1.0 (0.8–1.2)	1.1 (0.9–1.4)	2.2 (1.6–3.0)	3.4 (2.0–5.9)
CKD-EPI	1.2 (0.9–1.6)	1 (ref)	0.9 (0.8–1.1)	1.1 (0.9–1.3)	2.0 (1.5–2.7)	3.3 (2.0–5.5)
Cardiovascular mortality						
MDRD	1.4 (0.9–2.1)	1 (ref)	1.0 (0.7–1.4)	1.7 (1.1–2.5)	3.7 (2.2–6.2)	3.5 (1.2–10.0)
CKD-EPI	1.5 (0.9–2.6)	1 (ref)	0.9 (0.6–1.3)	1.6 (1.1–2.3)	3.1 (1.8–5.0)	4.3 (1.8–10.2)
No of men						
MDRD	773	1240	1008	337	64	14
CKD-EPI	417	1664	918	350	70	17
All-cause mortality						
MDRD	1.1 (0.9–1.5)	1 (ref)	1.0 (0.8–1.3)	1.1 (0.8–1.5)	2.5 (1.6–3.8)	2.5 (1.2–5.5)
CKD-EPI	1.3 (0.9–1.8)	1 (ref)	0.9 (0.7–1.1)	1.1 (0.8–1.4)	2.0 (1.3–3.1)	2.9 (1.5–5.5)
Cardiovascular mortality						
MDRD	1.5 (0.9–2.4)	1 (ref)	1.2 (0.7–1.9)	1.6 (0.9–2.7)	5.2 (2.6–10.3)	1.3 (0.2–10.0)
CKD-EPI	1.5 (0.8–2.7)	1 (ref)	0.9 (0.6–1.4)	1.4 (0.9–2.3)	3.4 (1.7–6.8)	3.1 (0.9–10.2)
No of women						
MDRD	685	1778	2024	645	118	11
CKD-EPI	471	2411	1694	553	119	13
All-cause mortality						
MDRD	1.2 (0.8–1.7)	1 (ref)	1.0 (0.8–1.3)	1.2 (0.9–1.7)	2.1 (1.3–3.2)	6.8 (3.1–15.0)
CKD-EPI	0.9 (0.5–1.5)	1 (ref)	1.0 (0.8–1.3)	1.1 (0.8–1.5)	2.0 (1.3–3.0)	4.9 (2.2–10.8)
Cardiovascular mortality						
MDRD	1.1 (0.5–2.3)	1 (ref)	0.7 (0.4–1.3)	1.7 (0.9–3.0)	2.5 (1.1–5.5)	8.6 (2.4–31.0)
CKD-EPI	1.3 (0.5–3.9)	1 (ref)	0.8 (0.5–1.4)	1.8 (1.0–3.1)	2.8 (1.3–5.8)	7.4 (2.1–26.6)

[a]Adjusted for age, sex, city, annual income, smoking, history of cardiovascular disease, BMI, hypertension, diabetes, hypercholesterolaemia and use of renin–angiotensin system inhibitors. eGFR, glomerular filtration rate estimated with both the Modification of Diet in Renal Disease (MDRD) study and the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equations.

prevalence was also 27.9%; it was 7.2% for Stages 1–2, 15.4% for 3A and 5.3% for 3B or higher.

Discussion

Knowledge of the specific aspects of CKD epidemiology in the elderly is essential to implement appropriate management. The determination of eGFR distribution for old and very old people, based on IDMS traceable serum creatinine and appropriate equations, is thus an important step forward. This study showed that impaired kidney function was associated with excess mortality with very similar risk estimates using the MDRD or the CKD-EPI equations. Moreover, more than one of six individuals in this population had fast eGFR decline rate, >4 mL/min/1.73m^2. The most original findings indicate that only a fraction of those with decreased eGFR have markers of kidney damage and that others than proteinuria should be considered to assess its clinical significance in the elderly.

The large sample size of this population and the low number of participants lost to follow-up (8 of 8705 at 6 years) are major strengths of this study. Other strengths include the use of standardized measures of creatinine over 4 years, which reduced systematic bias in the estimate of eGFR decline. This study also has limitations. First, the participation rate was low, and those who participated differed somewhat in age and sex distribution as compared with the general population aged 65 years and over in the three towns [43]. Moreover, the recruitment procedure led to the selection of urban participants only, who also had a higher socioeconomic levels than the overall French population. Although this might have led to underestimation of CKD prevalence, it should not have biased the relations between eGFR level and the studied markers and outcomes. Second, data on ethnicity were not available to calculate eGFR. Because elderly people selected from these cities' electoral rolls are unlikely to be of African origin, this factor should have minimal impact on eGFR estimates, but our reference values are only generalizable to European elderly. Third, baseline data on ACR/PCR would have been valuable to assess the independent impact on decline and mortality and to assess risk stratification using eGFR and ACR. Fourth, 26% of Bordeaux participants alive at 4 years declined the follow-up study. They differ slightly from those included with respect to age and sex but were highly comparable for the other baseline data including eGFR. This may have decreased study power, particularly in the subgroup analyses, but is unlikely to have systematically biased our estimates of eGFR decline. In contrast,

Table 5. eGFR decline using the MDRD study equation according to baseline characteristics and participant mean eGFR in the subsample with 4-year follow-up

		Crude eGFR decline (mL/min/1.73m^2/year)		Adjusted eGFR decline[a] (mL/min/1.73m^2/year)	
	N	% >4	Mean ± SD	Mean (95% CI)	P
All	1298	17.4	1.46 ± 2.87	1.46 (1.30–1.61)	
Age (years)					
65–70	303	14.5	1.16 ± 2.60	1.15 (0.83–1.48)	0.19
70–75	458	17.9	1.55 ± 2.87	1.56 (1.30–1.82)	
75–80	354	19.2	1.61 ± 2.99	1.59 (1.29–1.89)	
≥80	183	17.5	1.40 ± 3.06	1.42 (1.00–1.84)	
Men	474	20.7	1.83 ± 2.89	1.78 (1.52–2.04)	0.0025
Women	824	15.5	1.24 ± 2.84	1.27 (1.07–1.47)	
Diabetes[b]					
No	1151	15.7	1.33 ± 2.81	1.34 (1.17–1.50)	0.0002
Yes	123	34.1	2.56 ± 3.23	2.45 (1.95–2.96)	
Unknown	24	12.5	1.86 ± 2.91	1.91 (0.77–3.05)	
Hypertension and BP in mmHg					
No	288	12.8	1.23 ± 2.54	1.34 (1.00–1.67)	0.35
Yes, treated					
BP < 140/90	270	19.3	1.40 ± 3.03	1.37 (1.03–1.71)	
140/90 ≤ BP < 160/95	400	15.0	1.39 ± 2.85	1.39 (1.11–1.67)	
BP ≥ 160/95	340	22.6	1.78 ± 3.02	1.70 (1.39–2.00)	
Participant mean eGFR in mL/min/1.73m^2					
≥75	670	19.0	1.44 ± 2.99	1.41 (1.20–1.63)	0.68
60–75	430	15.3	1.39 ± 2.71	1.44 (1.17–1.71)	
45–60	169	16.0	1.68 ± 2.76	1.70 (1.27–2.13)	
<45	29	20.7	1.45 ± 3.26	1.26 (0.21–2.31)	

[a]Adjusted for age, sex, diabetes, hypertension and participant mean eGFR over 4 years.
[b]Diabetes was self-reported or defined as fasting glycaemia ≥7 mmol/L or nonfasting glycaemia ≥11 mmol/L or antidiabetic drug use.

the 137 participants who died within 4 years are likely to be those with more rapid decline [29], and this may have underestimated the observed rate. Finally, eGFR decline rate was assessed based on only two creatinine measurements which may have reduced the accuracy of estimates, but other sources of inaccuracy were well controlled: creatinine measurements were standardized over the study period, and adjustment for individual mean eGFR should have reduced regression to the mean [48, 49].

It is well established that kidney function decreases with age, but the magnitude of normal decline, measured by a reference method, is unknown in the oldest groups. Our age- and sex-specific mean MDRD eGFR values in participants without CKD risk factors were 7–12 mL/min/1.73m^2 higher than those provided in 869 Dutch subjects aged 65 years or older, free from kidney or cardiovascular disease, hypertension and diabetes [18]. This is likely to be due to the use of non-IDMS traceable creatinine and early MDRD equation in the Dutch study [18], which underestimates true GFR at higher levels [40]. Another likely explanation may be a healthier profile in the 3C population. As expected, eGFR values with either equation were lower in those with than without CKD risk factors, and differences tended to widen with age and in men compared with women. In contrast with what was observed in the middle-aged population of the Atherosclerosis Risk in Communities (ARIC) study, the CKD-EPI equation reclassified upward <10% of the 3C participants with MDRD eGFR <60 mL/min/1.73 m^2 versus about 45% in ARIC participants [42], resulting in little impact on the prevalence of CKD Stage 3 or higher, 12.9 versus 13.7%. On the opposite side, while only those with MDRD eGFR >120 mL/min/1.73m^2 were reclassified downward with the CKD-EPI equation in the ARIC study, this was observed in nearly 50% of the 3C participants with MDRD eGFR >90, resulting in lesser discrimination in the upper range of eGFR values. As previously noticed from the properties of the CKD-EPI equation compared with the MDRD equation, the gradient with age was steeper, and differences between men and women at each age were smaller [40].

Few population-based studies have investigated eGFR changes over time [27–29]. Our annual rates of eGFR decline, i.e. 1.46 mL/min/1.73m^2/year with the MDRD equation and 1.53 with CKD-EPI, was similar to that observed in The Longitudinal Aging Study [27], i.e. 1.49 mL/min/year based on creatinine clearance in the 70- to 79-year olds, but was greater than in the Cardiovascular Health Study (CHS) elderly population, 0.4 mL/min/1.73m^2/year [29]. Differences in creatinine assays and eGFR equations between studies probably explain this discrepancy. As in another community-dwelling elderly cohort [28], eGFR declined faster in men than in women, in those with than without diabetes, but no trend appeared as individual mean eGFR decreased. Although there was a trend toward steeper decline in those with poorer BP control, the association was nonsignificant in this population. The K/DOQI [3] defines decline rates >4 mL/min/1.73m^2/year as 'fast', as individuals with eGFR <60 mL/min/1.73m^2 might reach end-stage kidney disease within 10 years. This was found in 17% of the 3C participants. In contrast, the UK NICE

defines progression as a decline >5 mL/min/1.73m^2 within 1 year or >10 mL/min/1.73m^2 within 5 years [22]. More than a third of 3C participants had an annual decline >2 mL/min/1.73m^2, i.e. 10 in 5 years, but 9.9% >5 mL/min/1.73m^2, which is slightly higher than the 6.8% observed in the UK East Kent population aged 70–80 years old [50]. Although it is well known that mortality risk outweighs that of end-stage kidney disease [35, 36, 51], this percentage may more closely assess the fraction of the elderly population with significant CKD progression to be targeted for nephrological assessment and management.

Several studies have shown that the mortality risk associated with a given eGFR level is attenuated in the elderly [14, 34, 38, 39, 52]. In younger individuals, mortality risk exceeds that of their reference category at an eGFR of 60 mL/min/1.73m^2, but in those older than 75 years, the relevant eGFR would be closer to 45 mL/min/1.73m^2 [38]. Our results are consistent with these studies when using the MDRD equation to estimate GFR. Using the CKD-EPI equation provided very similar HR estimates, but in women, that for cardiovascular mortality in those with an eGFR of 45–60 mL/min/1.73m^2 was of borderline significance.

This study assessed the severity of kidney damage, based on current recommended criteria for specialist referral and available evidence that treatment can improve patient outcomes [3, 22–24]. As previously observed [5], microalbuminuria was common but was associated with diabetes in only one-third of cases. Although microalbuminuria is a well-established risk factor of both end-stage kidney disease and death [37, 39, 53, 54], only in this latter case is it targeted by therapeutic guidelines [3, 22, 55, 56]. In contrast, clinical proteinuria, a modifiable risk factor for CKD progression [22], was uncommon above an eGFR of 45 mL/min/1.73m^2, which is consistent with findings for older adults in the USA [56]. Another sign of disease severity requiring specialist referral is resistant hypertension, defined by the 2004 K/DOQI as poor BP control despite the use of at least three antihypertensive drugs [23, 57]. Whereas several studies have shown that a high prevalence of uncontrolled BP among those with CKD [58–60] that of resistant hypertension has not been specifically assessed. Here, it affected 6% of those at CKD Stage 3A and 16% at Stage 3B or higher. K/DOQI defined anaemia [24] is also an early and severe CKD complication [25, 26]. Though less common than resistant hypertension, anaemia may help identify elderly people with true but poorly proteinuric CKD. Finally, disproportionately high rates of CKD Stage 3 as compared with Stages 1–2 were often observed in the elderly, e.g. 38 versus 10% in NHANES, an odd finding, which nourished the controversies about its clinical significance [56]. Although such disproportion was not seen in the 3C study with either equation, it is clear that kidney markers together with eGFR level provided a more relevant distribution for disease severity stages than previously observed in the older population.

In conclusion, we have shown that the CKD-EPI equation may not improve categorization of elderly people with respect to CKD and long-term mortality risk compared with the MDRD equation. Only a fraction of those with impaired function, higher in men than in women, have markers of kidney damage and who might deserve specialist assessment and appropriate care. In the elderly, the focus of referral could be on eGFR <45 mL/min/1.73m^2 with anaemia, resistant hypertension or clinical proteinuria, in addition to microalbuminuria in the presence of diabetes.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

Acknowledgements. We thank Jo Ann Cahn for the English revision of this manuscript.
Funding. The 3C study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale (Inserm), the Victor Segalen-Bordeaux 2 University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C study was also supported by the Caisse Nationale d′Assurance Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l' Education Nationale, Institut de la Longévité, Conseils Régionaux d Aquitaine et Bourgogne, Fondation de France, and Ministry of Research-INSERM Program "Cohortes et collections de données biologiques". The CKD substudy was supported by grants from the Société de Néphrologie, Inserm program « Réseaux de recherche » (A08058LS) and GIS-IReSP Research program "Trés grandes infrastructures de recherche" (AO 08113LS).

Conflict of interest statement. None declared.

(See related article by Roderick. Chronic kidney disease in older people: a cause for concern? *Nephrol Dial Transplant* 2011; 26: 3083–3085.)

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Received for publication: 31.1.11; Accepted in revised form: 9.5.11