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

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– The Three-City prospective cohort study

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Abstract

Background. Little is known about normal kidney function level and the prognosissignificance 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 ≥ 65 years and studied its relation to 6-year mortality. In a subsample of 1298 examined at 4 yrs, we assessed annual eGFR decline and clinically relevant markers including microalbuminuria (3-30 mg/mmolcreatinine) with diabetes, proteinuria ≥50 mg/mmol, haemoglobin<11 g/L, or resistant hypertension despite 3 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< 60mL/min/1.73m^2 was13.7%, and of CKD-EPI eGFR, 12.9%. After adjustment for several confounders, only those with an eGFR<45 mL/min/1.73 m^2 had significantly higher all-cause and cardiovascular mortality than thosewith an eGFR of 75 to 89 mL/min/1.73 m^2 whatever the equation. In subsample men and women with 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 women, 1.75 *vs* 1.41 mL/min/1.73m^2 per year.

Conclusion. Moderately decreased eGFR is more often associated with clinical markers in men than 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.

Key words chronic kidney disease, glomerular filtration rate, elderly, mortality, proteinuriaanaemia

S**hort summary**

Impaired kidney function is common in the elderly, but its clinical and prognosis significancehas been poorly assessed so far. In both sexes, an estimated GFR < 45 mL/min/1.73m^2 is related to increased all-cause and cardiovascular mortality. Only a fraction of the elderly with moderately impaired function, higher in men than women, have markers of kidney damage who might deserve specialist assessment. In addition to proteinuria, resistant hypertension and anaemia should be considered to appraise the clinical significance of kidney impairment in the elderly.

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 programs.[1,2][3] Routine reporting of estimated glomerular filtration rate (eGFR) has led to label up to nearly half of the elderly as having CKD [4-7] and 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/1.73 m^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] in the older people.[21,26] Data on eGFR change over time is 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 age attenuates these associations.[35-39] Finally, use of creatinine enzymatic assay and development of new equations improved eGFR assessment, but while the CKD Epidemiology Collaboration (CKD-EPI)[40] equation has shown to better categorized 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-specificeGFR 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.

Subjects 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 Bordeauxwas also seen at four years, to assess eGFR decline and CKD markers (Figure 1).

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 WHO'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 minutes rest and averaged. Hypertension was defined by a mean systolic BP ≥140 or diastolic BP ≥90 mm Hg,[45] or by the use of antihypertensive drugs. Resistant hypertension was defined as a mean systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg 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 mm Hg.[23]. Diabetes was either self-reported or defined as fasting glucose ≥ 7 mmol/L or non-fasting ≥ 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 wereremeasured 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 x $S_{crJaffe}$ + 4.40; (2) S_{crIDMS}= 0.87 x $S_{crJaffe}$ + 7.85.

We calculated eGFR in mL/min/1.73 m^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 sub-sample, 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 and the mean of baseline and 4-year eGFR values to classify individuals. CKD stage 1-2 was defined as a mean eGFR ≥ 60 mL/min/1.73 m^2 with ACR≥ 3 mg/mmolor clinical proteinuria; stage 3A, as an eGFR of 45-59, and 3B or higher, as eGFR< 45.

Mortality

Six-year mortality was assessed by active follow-up of all participants. It remained unknown for only 8 participants. Causes of deathwereascertained by an adjudication committeeusing all availablemedical data fromhospitals, familyphysicians or specialists, and proxy interviews as reportedearlier[Ref]

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-reportedkidney 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 (HR) associated with MDRD- and CKD-EPI- eGFR per 15 mL/min/1.73 m^2 stratum were then estimated in the overall population and by sex with Cox models and eGFR of 75 to 89 as the reference category. The 8 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/1.73 m^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 eGFRvalues. The percentages of participants with eGFR decline rate >4ml/min/1.73m^2 are alsoshownaccording to thesefactors. [Ref 3]Finally, we studied the prevalence of each kidney markers according to ~~mean~~MDRD-eGFR at 4 years. We also evaluated the prevalence of CKD stages at 4 yrs 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 anemia), 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).

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/1.73 m^2 and CKD-EPI eGFRs from 16 to 109, for serum creatinine values from 32 to 322 µmol/L (Table 2 and Supp Table). Gradient for age was steeper with the CKD-EPI than the MDRD equation. Mean eGFR was higher in men than 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/1.73 m^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).

Hazard ratios for 6-year mortality related to baseline eGFR

After adjustment for several confounders, only those with an eGFR<45 mL/min/1.73m^2had significantly higher all-cause mortality than those with an eGFR of 75 to 89, in both men and women and with either equation. (Table 3) Cardiovascular mortality significantly exceeded that of the reference group foreGFRs<60 mL/min/1.73 m^2 in the overall population, but for each sex taken separately, it significantly exceeded only for eGFR<45 mL/min/1.73 m^2.

Estimated GFR 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 four out of ten by > 2 mL/min/1.73 m^2/yr, one out of six by > 4, and in 10% by > 5 mL/min/1.73 m^2/yr. The adjusted mean annual decline was significantly steeper in men than 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 towards steeper decline with increasing blood pressure in those with hypertension. Mean CKD-EPI eGFR decline was 1.53±2.35 mL/min/1.73 m^2/yr, and was similarly related with studied factors (data not shown).

Prevalence of kidney damage markers according to mean MDRD eGFR level

In the sub sample, as MDRD eGFR decreased from ≥75 to <45 mL/min/1.73 m^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 sub sample,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% *vs* 5.7%;it was closer for other stages: 15.1 vs 16.9% for stage 3A, and 5.7% *vs* 3.9% for stage 3B or higher. Using CKD-EPI, the overall 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 out of six individuals in this population had fast eGFR decline rate, > 4 mL/min/1.73 m2. 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 out of 8,705 at six 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 differedsomewhat in age and sex distribution as comparedwith the general population aged 65 years and over in the threetowns.[43]Moreover, the recruitmentprocedureled to the selection of urban participants only, whoalsohada higher socioeconomic levels than the overall French population. Although this might have led to underestimate CKD prevalence, it should not have biased the relations between eGFRlevel 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 ~~or North African~~ elderly. Third, baseline data on ACR/PCR would have been valuable to assess the independent impact on decline and mortality and to assessrisk stratification usingeGFR 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, 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.[47,48]

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/1.73 m^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 less than 10% of the 3C participants with MDRD eGFR less than 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 *vs* 13.7%. On the opposite side, while only those with MDRD eGFR> 120 mL/min/1.73 m^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, 1.46 mL/min/1.73 m^2 per year with the MDRD equation and 1.53 with CKD-EPI, compared with the 1.49 mL/min per year based on creatinine clearance in the 70-79 year-olds from The Longitudinal Aging Study,[27] but was greater than in the Cardiovascular Health Study (CHS) elderly population, 0.4 mL/min/1.73 m^2 per 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 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 higher than 4 mL/min/1.73 m^2 per year as "fast", as individuals with eGFR<60 mL/min/1.73 m^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/1.73 m^2 within one year or >10 mL/min/1.73 m^2 within 5 years.[22] More than a third of 3C participants had an annual decline >2 mL/min/1.73 m^2, i.e., 10 in 5 years, but 9.9% > 5 mL/min/1.73 m^2, which is slightly higher than the 6.8% observed in the UK East Kent population aged 70 to 80 years old.[51] Although it is well-known that mortality risk outweighs that of end-stage kidney disease,[35,36,52] this percentage may more closely assess the fraction of the elderly population with significant CKD progression to be targeted for management.

Several studies have shown that the mortality risk associated with a given eGFR level is attenuated in the elderly.[14,34,38,39,53] In younger individuals, mortality risk exceeds that of their reference category at an eGFR of 60 mL/min/1.73 m^2,[21] but in those older than 75, the relevant eGFR would be closer to 45 mL/min/1.73 m^2.[23] [38] Our results are consistent with these studies when using the MDRD equation to estimate GFR. Using the CKD-EPI equation provided very similar hazard ratio estimates, but in women, that for cardiovascular mortality in those with an eGFR of 45 to 60 mL/min/1.73 m^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,[37,39,54,55] only in this latter case is it targeted by therapeutic guidelines.[3,22,56,57] In contrast, clinical proteinuria, a modifiable risk factor for CKD progression,[22] was uncommon above an eGFR of 45 mL/min/1.73 m^2, which is consistent with findings for older adults in the US.[57] 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.[23,58] Whereas several studies have shown a high prevalence of uncontrolled BP among those with CKD,[59-61] 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% *vs* 10% in NHANES,[3] an odd finding which nourished the controversies about its clinical significance.[57] 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 previoulsy 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 women, have markers of kidney damagewho might deserve specialist assessment and appropriate care.This study provides evidence that markers other than proteinuriaare needed to distinguish aging kidneys from true CKD and avoid unnecessary referrals in the elderly with moderately decreased eGFR, particularly in women.[62-64]

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The authors declare that they have no competing financial interest

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Table 1. Baseline characteristics of the Three-City study participants.

	Overall (8,705)	CKD risk factors or known kidney disease		Subsample with 4-year follow-up (1,298)
(N)		No (3,768)	Yes (4,937)	
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 (€/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
Hypercholesterolemia				
No	43.4	43.8	43.1	42.4
Yes,≥6.2 mmol/L not treated	26.5	30.5	23.5	26.1
Yes, treated	30.1	25.8	33.4	31.4
Diabetes†	9.7	-	17.1	9.7
Hypertension ‡	77.3	61.3	89.6	77.8
Blood pressure ≥ 160/100	26.3	-	46.4	23.7
Body mass index > 30 kg/m^2	13.2	-	23.3	17.4
History of cardiovascular disease	29.6	-	52.1	29.0
Known kidney disease	0.7	-	1.3	0.7
Use of reninangiotensin system inhibitor	22.9	13.9	29.7	22.6
Serum creatinine (micromol/L)	76.4±18.2	73.6±14.4	78.5±20.4	73.8 ± 17.3
MDRD eGFR in mL/min/1.73m²	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/1.73m²	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

Values are means ± sd or percent.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate
†Diabetes was either self-reported or defined as fasting glycemia ≥ 7 mmol/L or nonfastingglycemia ≥ 11 mmol/L orantidiabetic drug treatment.
‡Hypertension defined as blood pressure ≥140/90 mm Hg or antihypertensive drug treatment (stage 2 defined as blood pressure ≥ 160 /100 mm Hg with or without antihypertensive drug treatment) [45]

Table 2. Age- and sex-specific eGFR values in ml/min/1.73m² calculated with the MDRD and CKD-EPI equations in all participants, and by sub-group

		All 3C participants						Participants without CKD risk factors* or known kidney disease						Participants with CKD risk factors* or known kidney disease					
	Age	N	Mean ± Std	Median	(Min-Max)	P5	Q1-Q3	N	Mean ± Std	Median	(Min-Max)	P5	Q1-Q3	N	Mean ± Std	Median	(Min-Max)	P5	Q1-Q3
eGFR MDRD																			
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

		All 3C participants						Participants without CKD risk factors* or known kidney disease						Participants with CKD risk factors* or known kidney disease					
	Age	**N**	**Mean ± Std**	**Median**	**(Min-Max)**	**P5**	**Q1-Q3**	**N**	**Mean ± Std**	**Median**	**(Min-Max)**	**P5**	**Q1-Q3**	**N**	**Mean ± Std**	**Median**	**(Min-Max)**	**P5**	**Q1-Q3**
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**
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**

eGFR: glomerular filtration rate estimated with the MDRD, Modification of Diet in Renal Disease Study, andthe CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration equations ; P5, Q1-Q3, are the 5thpercentile and interquartile range of the eGFR distribution

* Obesity, blood pressure ≥160/100, diabetes, cardiovascular history

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

		CKD-EPI eGFR (mL/min/1.73m²)					
		<30	**30 - 44**	**45-59**	**60-89**	**>90**	Total
MDRD eGFR (mL/min/1.73m²)	**<30**	25	0	0	0	0	25
		(0.3)	0	0	0	0	
	30-44	5	171	6	0	0	182
		(0.1)	(2.0)	(0.1)	0	0	
	45-59	0	18	849	117	0	984
		0	(0.2)	(9.8)	(1.3)	0	
	60-89	0	0	49	5,914	93	6,056
		0	0	(0.6)	(67.9)	(1.1)	
	>90	0	0	0	663	795	1,458
		0	0	0	(7.6)	(9.1)	
	Total	30	189	904	6,694	888	8,705

Note: *In theupper diagonal, eGFR CKD-EPI underestimates eGFR compared to MDRD study equation whereas it overestimates into the lower diagonal*

Abbreviations: 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

Table 4. Adjusted hazard ratios for 6-year all-cause and cardiovascular mortality related to baselineeGFR using either the MDRD or CKD-EPI equation, overall and by sex.

	eGFR in ml/min/1.73m²					
	≥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)

* adjusted for age, sex, city, annual income, smoking, history of cardiovascular disease, body mass index, hypertension, diabetes, hypercholesterolemia, and use of reninangiotensin 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

Table 5. Estimated GFR 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/ 1.73m²/yr)		Adjusted eGFR decline* (mL/min/1.73m²/yr)	
	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†					
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 mm Hg					
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/1.73 m²					
≥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)	

*adjusted for age, sex, diabetes, hypertension, and participant mean eGFR over 4 years
†Diabetes was self-reported or defined as fasting glycemia ≥ 7 mmol/L or nonfastingglycemia ≥ 11 mmol/L or antidiabetic drug use
eGFR : glomerular filtration rate estimated with the Modification of Diet in Renal Disease (MDRD) Study equation
BP :blood pressure

Figure legends

Figure 1 - Three-City Study flow chart

Figure 2 – Prevalence of kidney damage markers according toeGFR 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 blood pressure ≥ 130/80 mmHg for those with either an eGFR<60 mL/min/1.73 m², diabetes, proteinuria ≥ 50 mg/mmol or albuminuria ≥ 30 mg/mmol, otherwise the threshold was 140/90 mmHg. Anemia defined as an hemoglobin <11 g/dL

Figure 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 hemoglobin <11 g/dL, and resistant hypertension defined as a blood pressure ≥ 130/80 mmHg for those with either an eGFR<60 mL/min/1.73 m², diabetes, proteinuria ≥ 50 mg/mmol or albuminuria ≥ 30 mg/mmol, otherwise the threshold was 140/90 mmHg.

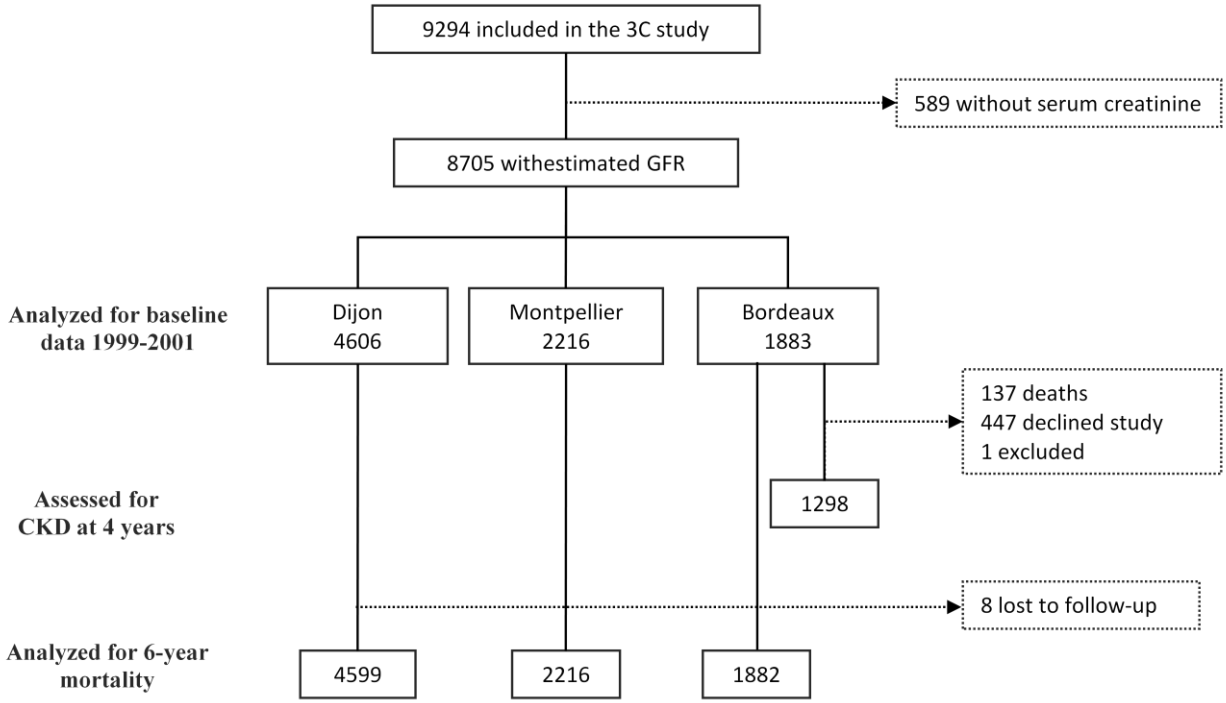
9294 included in the 3C study
589 without serum creatinine
8705 withestimated GFR
Analyzed for baseline data 1999-2001
Dijon 4606
Montpellier 2216
Bordeaux 1883
137 deaths
447 declined study
1 excluded
Assessed for CKD at 4 years
1298
8 lost to follow-up
Analyzed for 6-year mortality
4599
2216
1882

Figure 1

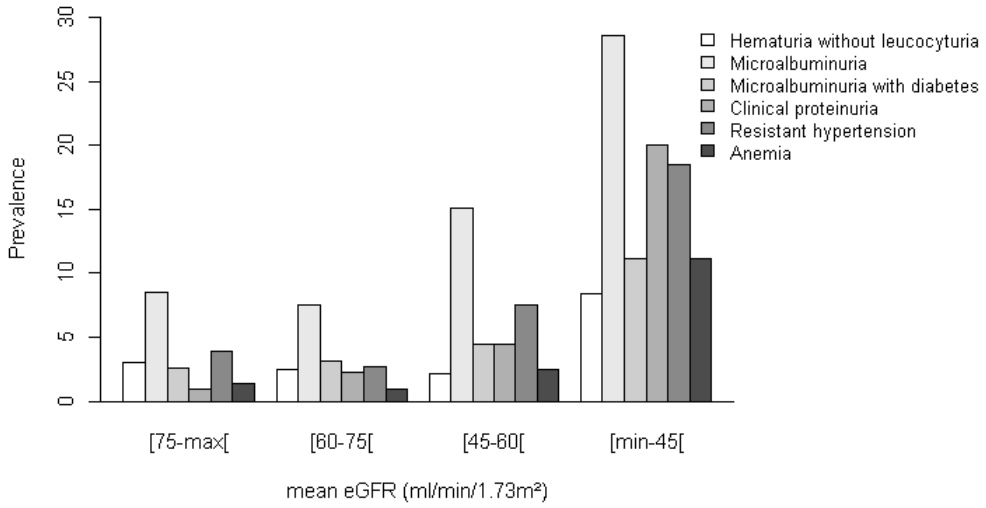
Prevalence
0
5
10
15
20
25
30
[75-max[
[60-75[
[45-60[
[min-45[
mean eGFR (ml/min/1.73m²)
Hematuria without leucocyturia
Microalbuminuria
Microalbuminuria with diabetes
Clinical proteinuria
Resistant hypertension
Anemia

Figure 2

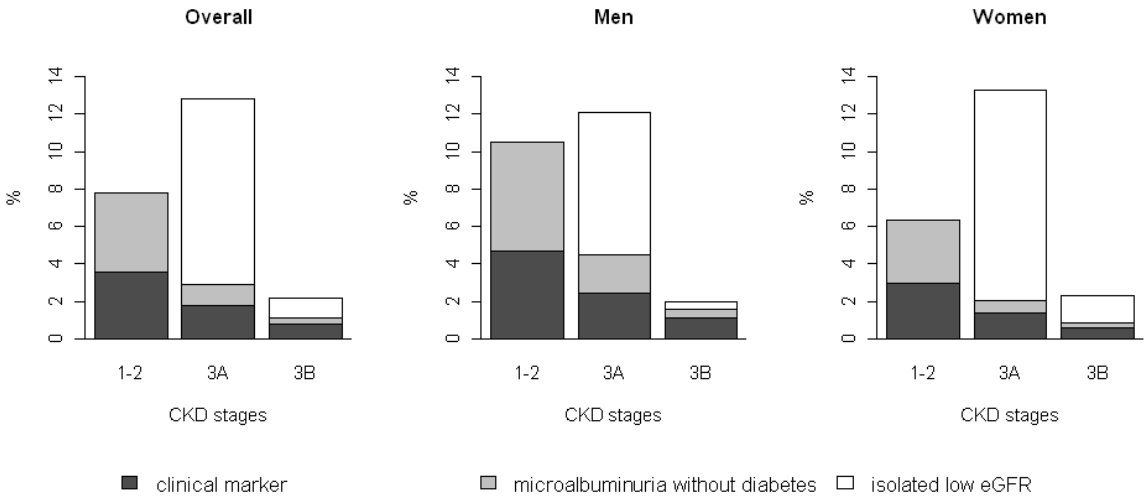
Overall
Men
Women
%
0 2 4 6 8 10 12 14
1-2
3A
3B
CKD stages
clinical marker
microalbuminuria without diabetes
isolated low eGFR

Figure 3