Natural History of Older Adults with Impaired Kidney Function: The InCHIANTI Study

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Abstract

The aim of this study was to assess the kidney function of an older community-dwelling population at baseline and appraise its evolution after 3 years of follow-up in terms of chronic kidney disease (CKD) stage progression, magnitude of glomerular filtration rate (GFR) changes, and value of serum creatinine. This was a prospective population-based study of 676 Italian participants, aged 65 years and older. GFR was estimated using the Cockcroft–Gault equation and the Modification of Diet in Renal Disease Study equation. Using the Cockcroft–Gault equation. A total of 33% of participants had criteria of CKD (GFR < 60 mL/min) at baseline; among them, the majority remained stable, 10% improved, and 7% progressed to more severe CKD stages at follow-up. Loss of GFR in participants with GFR < 60 mL/min was significantly lower (1.4 mL/min per year) than in participants with GFR ≥ 60 mL/min (3.3 mL/min per year) at baseline. Most participants classified with CKD stage 2 (GFR 60–89 mL/min) or stage 3 (GFR 30–59 mL/min) at baseline did not change stage, whereas 55% of people with CKD stage 1 (GFR > 90 mL/min) at baseline worsened to stage 2 and 10% worsened to stage 3. An abnormal high level of serum creatinine at baseline did not help to predict who might worsen at follow-up. Older people with CKD displayed a low progression of renal disease and therefore are at higher risk for comorbidities related to CKD than for progression to end-stage renal disease.

Introduction

CHRONIC KIDNEY DISEASE (CKD) is an important public health problem especially in older age. In a representative noninstitutionalized U.S. population over 70 years of age, the prevalence of CKD stage 3 (glomerular filtration rate [GFR] 30–59 mL/min per 1.73 m²) and 4 (GFR 15–29 mL/min per 1.73 m²) was 37.8% as estimated with the Modification of Diet in Renal Disease Study equation (MDRD).¹ In an Italian population sample, the prevalence of CKD defined as GFR < 60 mL/min per 1.73 m² using the MDRD equation was 15% and 11% for men and women, respectively, aged 65–74, and 34.5% and 31.6% for men and women, respectively, over 75 years of age, a prevalence close to the one found in the U.S. population.²

Older age represents a risk factor for CKD, and CKD has been associated with higher morbidity,^{3,4} greater health care utilization,^{5–8} and higher mortality.^{7,9} In older people, level of kidney function (KF) as well as rapid decline in KF have been shown to be both independent risk factors for cardiovascular disease (CVD), new onset of CVD, and all-cause

mortality.^{10–12} However, CKD diagnosis is less obvious in older persons than in younger adults. Indeed, the majority (76.3%) of the total InCHIANTI (Invecchiare in Chianti [Aging in the Chianti Area]) Study sample over 65 years with GFR < 60 mL/min had normal serum creatinine levels.¹³

Previous studies have shown that there is a progressive decline in GFR with age.^{14,15} These studies display only the overall mean of GFR decline as if there were a progressive, homogeneous, and irreversible decline in KF with age. However, one study assessing the creatinine clearance of 446 community-dwelling men aged 22–97 years found that 156 (35%) subjects presented no decrease in KF.¹⁴ Indeed, the practice experience demonstrates that patients, especially older people, are not homogeneous, and that different patterns of KF history may exist.

The aim of the current study was to assess the KF of an older community-dwelling population at baseline and appraise its evolution at 3 years of follow-up in terms of CKD stage progression, magnitude of GFR changes, and value of serum creatinine.

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Methods

Study design and population

This study used baseline and 3 years of follow-up data from the InCHIANTI Study, a longitudinal population-based study of people living in Greve in Chianti and Bagno a Ripoli, in the Tuscany region of Italy. This study was planned by the Laboratory of Clinical Epidemiology of the Italian National Research Council on Aging (INRCA, Florence, Italy) in collaboration with the Laboratory of Epidemiology, Demography, and Biometry at the National Institute on Aging. Data were collected between September, 1998 and March 2000 for baseline and between November, 2001 and November, 2003 for follow-up. The INRCA ethics committee approved the InCHIANTI Study protocol, which met the criteria outlined in the Declaration of Helsinki. All subjects agreed to participate in the study and provided informed consent.

Figure 1 shows the different recruitment steps from the total InCHIANTI Study population to the analytic sample size. The InCHIANTI Study included 1,453 people who were randomly selected using a multistage stratified sampling method; they agreed to participate in the study and provided written informed consent. Participants below 65 years ($n = 298$), with missing values of serum creatinine and/or weight at baseline ($n = 176$) or follow-up ($n = 146$), and participants missing at follow-up ($n = 157$) were excluded, leading to a total sample size of 676 participants.

Excluded people 65 years and over, were older, predominantly women, and displayed lower GFR, years of educa-

tion, score on the Mini-Mental State Examination (MMSE) and had worse physical performance and more co-morbidities. Excluded people due to missing values at follow-up or loss to follow-up (303 participants) displayed a mean GFR of 57.7 mL/min (GFR ≥ 60 mL/min in 43%; GFR 30–59 in 51%; GFR 15–29 in 6%). Causes of death, defined using International Classification of Diseases (ICD)-9 code, were mainly due to circulatory system disease (51%), neoplasm (28%), respiratory system disease (7%), nervous system disease (4%), senility (3%), and other diseases (7%). No participants died due to end-stage CKD.

Data collection

Participants underwent a first interview at home during which sociodemographic data were collected and cognitive performance was assessed using the MMSE.¹⁶ The number of years the subject attended school was used to define education. During a second appointment at the study clinic, participants who fasted at least 8 hr underwent a peripheral blood collection. The clinical examination occurred during a third visit and was carried out by trained geriatricians and physical therapists. The presence and severity of co-morbidities found during the examination were verified using standard algorithms based on medical history, drug treatments, symptoms and signs, medical documents, and hospital discharge records.¹⁷ Weight and height were measured with participants wearing light clothes and no shoes, and used to compute body mass index (BMI) as (weight [kg]/(height [m])²). Blood pressure was first assessed on both arms with the patient supine for at least 5 min. Then measurements were repeated two times on the arm with the highest value of systolic blood pressure (SBP), and the mean of these two values was used to define SBP. Physical function was assessed using the Short Physical Performance Battery.¹⁸

Laboratory measures and kidney function assessment

Serum creatinine was detected by kinetic-colorimetric assay based on a modified Jaffe method using a commercial enzymatic kit (Roche Diagnostics, GmbH, Mannheim, Germany) and Roche-Hitachi Analyzer in the same central laboratory at baseline and follow-up. The analytical sensitivity (lower detection limit) was 0.1 mg/dL, with intraassay and interassay coefficients of variation of 0.7% and 2.3%, respectively. Serum creatinine was used to estimate the GFR and to stratify the population between normal and abnormal serum creatinine using previously established cutoffs for adults [abnormal values: men, > 1.3 mg/dL (> 114.9 μ mol/L); women > 1.0 mg/dL (> 88.4 μ mol/L)].¹⁹

Both the Cockcroft–Gault (CG) and MDRD equations have been proposed as good estimates of GFR in an adult population by the Kidney Disease Outcome Quality Initiative of the National Kidney Foundation (NKF-K/DOQI).⁴ However, it has been shown that in older populations, and when using the serum creatinine assay not calibrated to the new criterion standard, the CG equation constantly underestimates the true GFR^{20–25} compared to the MDRD equation, which displayed less consistent results, with both underestimation^{20,21,25} and overestimation^{22–24} of the true GFR.^{13,26} Furthermore, CG is still widely used in clinics and has not yet been supplemented by MDRD in terms of GFR assessment for drug dosage adjustment. A new equation to esti-

FIG. 1. Recruitment of the population.

mate GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,²⁷ has recently been developed in a large population but included few elderly people. None of these equations has been validated in an older population, and for these reasons CG was used in this study.

However, some analyses were also performed with the MDRD equation to compare results. Because results obtained with MDRD are adjusted to body surface area (BSA), we compared CG subgroup stratification with CG subgroup stratification adjusted to BSA. Equations 1 and 2 (see Appendix) show CG²⁸ and MDRD²⁹ equations, respectively, to compute GFR. Equation 3 displays the CG equation adjusted to BSA.³⁰

Results were stratified into five categories of KF according to stages of CKD established by NKF-K/DOQI: Normal KF (GFR ≥ 90 mL/min) or Stage 1, mild KF impairment (GFR 60–89 mL/min) or Stage 2, moderate KF impairment (GFR 30–59 mL/min) or Stage 3, severe KF impairment (GFR 15–29 mL/min) or Stage 4, and terminal kidney failure (GFR < 15 mL/min) or Stage 5. CKD is defined by NKF-K/DOQI guidelines as GFR less than 60 mL/min or the presence of kidney damage defined by structural or functional abnormalities of the kidney, for 3 months or more.⁴

Statistical analyses

Excluded people aged 65 and older were compared to included participants according to demographics characteristics, anthropometrics, KF, chronic disease status, treatment for high blood pressure, and physical and cognitive function using multiple regression analysis for continuous dependent variables and logistic regression analysis for dichotomous dependent variables. The studied population was then stratified into four subgroups according to their GFR values at baseline and 3 years of follow-up: High-High (HH), GFR ≥ 60 mL/min at baseline and follow-up; High-Low (HL), GFR ≥ 60 mL/min at baseline and GFR < 60 mL/min at follow-up; Low-High (LH), GFR < 60 mL/min at baseline and GFR ≥ 60 mL/min at follow-up; Low-Low (LL), GFR < 60 mL/min at baseline and at follow-up. Characteristics of HL, LH, and LL were compared to those of HH using multiple regression analysis for continuous dependent variable and logistic regression analysis for dichotomous dependent variable unadjusted and adjusted for age and gender.

To understand the magnitude of change in KF among these four subgroups, a new continuous variable “delta” was created and defined as GFR at follow-up minus GFR at baseline. To facilitate comparison with the literature, we computed delta on a yearly basis, dividing delta by 3. Delta values of participants with GFR < 60 mL/min were compared to those with GFR ≥ 60 mL/min at baseline, and delta values of HL, LH, and LL were then compared to HH, using multiple regression analysis, unadjusted and adjusted for age and gender. Delta values were also plotted against GFR at baseline along with a quadratic regression curve and its 95% confidence interval. The coefficient of determination was used to assess the amount of variance in delta explained by the GFR at baseline. A likelihood ratio test was used to compare the linear and quadratic fit regressions.

Factors associated with a GFR < 60 mL/min at follow-up were assessed using logistic regression in a univariate anal-

ysis, using one independent variable at a time, and an adjusted full model, including all variables simultaneously. To build the adjusted full model, baseline characteristics were used as indicator variable in a forward method using five models consecutively, each new model adding new variables to the previous model: Model I, including age in categories and sex; model II, serum creatinine (mg/dL) and presence of CKD at baseline (GFR < 60 mL/min versus GFR ≥ 60 mL/min using the CG equation); model III, cognitive performance (MMSE score) and education (years of school); model IV, physical performance (good Short Physical Performance Battery [SPPB 10–12] versus poor [SPPB < 10] performers); and model V, co-morbidities (number of co-morbidities and cardiovascular disease, such as stroke, ischemic cardiomyopathy, and peripheral arterial disease). All variables with p values < 0.2 or with clinical relevance were kept in the consecutive models and included in the final full model. All statistical analyses were performed using Stata version 11.1 (StataCorp, College Station, TX; 2009).

Results

Table 1 describes baseline characteristics of the 676 subjects stratified into four subgroups according to their GFR at baseline and 3 years of follow-up. Compared to HH ($n = 300$), all of the other subgroups were significantly older, had higher proportions of women, and had lower GFR, BMI, and education. Compared to HH, LL ($n = 199$) displayed lower scores of MMSE, lower physical performance, higher prevalence of congestive heart failure (CHF), and higher level of serum creatinine, which was, however, still in the normal range of values; HL ($n = 154$) and LL had significantly higher SBP. The proportion of people with abnormal values of serum creatinine was significantly higher in LH ($n = 23$) and LL compared to HH.

Figure 2A shows the stratification of the study population by GFR values using CG. From the 454 participants with baseline GFR ≥ 60 mL/min, 33.9% worsened at follow-up. From the 222 participants with baseline GFR < 60 mL/min, 10.4% improved and 89.6% remained mainly stable. Indeed 16 (7.2%) of the participants with a GFR < 60 mL/min at baseline worsened by one stage of CKD at follow-up.

Values of unadjusted mean delta are also shown in Fig. 2A. The total population displayed a mean delta of -2.7 mL/min per year (-3.3 mL/min per year for participants with GFR ≥ 60 mL/min, -1.4 mL/min per year for those with GFR < 60 mL/min at baseline, difference statistically significant unadjusted and adjusted for age and gender, $p < 0.001$). HL (-6.2 mL/min per year) and LH ($+3.8$ mL/min per year) were significantly different from HH while adjusting or not for age and gender. LL (-2.0 mL/min per year) was not different from HH.

Regarding serum creatinine levels, 4 (0.9%) participants with a GFR ≥ 60 mL/min at baseline had abnormal high-level values and 3 (75%) of them displayed a GFR < 60 mL/min at follow-up. Among participants with GFR < 60 mL/min at baseline, 42 (18.9%) had abnormal high level values, and of them and at follow-up 5 (11.9%) improved by one stage of CKD, 29 (69%) remained stable, and 8 (19.1%) worsened by one stage of CKD.

Figure 2B shows the stratification by GFR values using the MDRD equation. From the 607 participants with

TABLE 1. POPULATION CHARACTERISTICS AT BASELINE

Characteristics	Subgroup HH n = 300	Subgroup HL n = 154	p values: HL vs. HH	Subgroup LH n = 23	p values LH vs. HH	Subgroup LL n = 199	p values LL vs. HH	p values global
Age, mean $\pm$ SD	70.1 $\pm$ 3.8	72.1 $\pm$ 4.5	<0.001	73.9 $\pm$ 5.8	<0.001	77.1 $\pm$ 6.2	<0.001	<0.001
Women, n (%)	134 (44.7)	86.0 (55.8)	0.024	16.0 (69.6)	0.026	129.0 (64.8)	<0.001	<0.001
GFR, Cockcroft-Gault, mL/min, mean $\pm$ SD	81.5 $\pm$ 14.3	69.6 $\pm$ 9.7	<0.001	54.8 $\pm$ 5.2	<0.001	48.6 $\pm$ 7.3	<0.001	<0.001
Women serum creatinine mg/dL, mean $\pm$ SD	0.8 $\pm$ 0.1	0.8 $\pm$ 0.1	0.003	0.9 $\pm$ 0.1	<0.001	0.9 $\pm$ 0.2	<0.001	<0.001
Men serum creatinine mg/dL, mean $\pm$ SD	0.9 $\pm$ 0.1	1.0 $\pm$ 0.1	0.166	1.1 $\pm$ 0.2	0.006	1.1 $\pm$ 0.2	<0.001	<0.001
High level of serum creatinine, n (%)	1.0 $\pm$ 0.3	3.0 $\pm$ 2.0	0.124	5.0 $\pm$ 21.7	<0.001	37.0 $\pm$ 18.6	<0.001	<0.001
Body mass index kg/m ² , mean $\pm$ SD	28.8 $\pm$ 3.8	28.0 $\pm$ 3.7	0.031	26.7 $\pm$ 4.0	0.008	25.1 $\pm$ 3.4	<0.001	<0.001
Education, years of school, mean $\pm$ SD	6.2 $\pm$ 3.6	5.4 $\pm$ 2.7	0.014	4.8 $\pm$ 1.6	0.047	5.2 $\pm$ 3.2	<0.001	0.001
Mini-Mental State Exam, mean $\pm$ SD	26.3 $\pm$ 2.5	26.0 $\pm$ 2.4	0.251	25.4 $\pm$ 3.4	0.143	24.9 $\pm$ 3.4	<0.001	<0.001
Short Physical Performance Battery score, mean $\pm$ SD	11.0 $\pm$ 1.7	10.9 $\pm$ 2.0	0.715	10.5 $\pm$ 2.9	0.246	10.2 $\pm$ 2.2	<0.001	<0.001
Co-morbidities, number, mean $\pm$ SD	1.0 $\pm$ 1.1	1.1 $\pm$ 1.1	0.258	0.9 $\pm$ 1.3	0.633	1.2 $\pm$ 1.1	0.077	0.250
SBP, mmHg, mean $\pm$ SD	147.2 $\pm$ 18.2	152.6 $\pm$ 20.2	0.004	144.9 $\pm$ 15.3	0.571	151.1 $\pm$ 18.8	0.025	0.010
Treatment for high blood pressure, n (%)	108 (36.0)	49.0 (31.8)	0.375	17.0 (73.9)	0.001	73.0 (36.7)	0.876	0.002
Diabetes mellitus, n (%)	42 (14.0)	22.0 (14.3)	0.934	4.0 (17.4)	0.655	25.0 (12.6)	0.645	0.911
Stroke, n (%)	18 (6.0)	8.0 (5.2)	0.727	0.0 (0.0)	—	9.0 (4.5)	0.476	0.767
Ischemic cardiomyopathy, n (%)	26 (8.7)	13.0 (8.4)	0.935	4.0 (17.4)	0.175	24.0 (12.1)	0.218	0.376
Congestive heart failure, n (%)	43 (14.3)	30.0 (19.5)	0.159	5.0 (21.7)	0.340	48.0 (24.1)	0.006	0.050
Peripheral arterial disease, n (%)	41 (13.7)	23.0 (14.9)	0.713	3.0 (13.0)	0.933	36.0 (18.1)	0.182	0.596
Chronic obstructive pulmonary disease, n (%)	31 (10.3)	16.0 (10.4)	0.985	1.0 (4.4)	0.371	16.0 (8.0)	0.392	0.623
Arthritis, n (%)	85 (28.3)	50.0 (32.5)	0.362	3.0 (13.0)	0.125	61.0 (30.7)	0.577	0.216
Cancer, n (%)	16 (5.3)	12.0 (7.8)	0.305	0.0 (0.0)	—	15.0 (7.5)	0.320	0.487
Parkinson's disease, n (%)	5 (1.7)	2.0 (1.3)	0.764	1.0 (4.4)	0.377	4.0 (2.0)	0.778	0.819

HH, High-High; HL, High-Low; LH, Low-High; SD, standard deviation; GFR, glomerular filtration rate; SBP, systolic blood pressure.

FIG. 2. (A) Population's stratification by glomerular filtration rate (GFR) estimation using the Cockcroft–Gault equation (CG). (B) Population stratification by glomerular filtration rate (GFR) estimation using the Modification of Diet in Renal Disease Study equation (MDRD). CI, Confidence interval.

GFR ≥ 60 mL/min per 1.73 m^2 , 22.6% worsened at follow-up. From the 69 with GFR < 60 mL/min per 1.73 m^2 , 26.1% improved, and 73.9% remained mainly stable. Only 2 (2.9%) participants with a GFR < 60 mL/min per 1.73 m^2 at baseline worsened by one stage of CKD at follow-up.

The overall absolute loss of GFR of participants with GFR ≥ 60 mL/min per 1.73 m^2 ($n=607$) was higher (-2.1 mL/min per year) than the loss of GFR (-0.4 mL/min per year) of participants with GFR < 60 mL/min per 1.73 m^2 ($n=69$), with the difference statistically significant only with unadjusted for age and gender values ($p=0.0178$). Among participants with GFR ≥ 60 mL/min per 1.73 m^2 at baseline, no one had high abnormal serum creatinine levels at baseline.

Figure 3A shows, for each participant, GFR at 3 years of follow-up (y axis) according to GFR at baseline (x axis) using the CG. Overall, GFR worsened for the majority of the population after 3 years (majority of circles under the identity line), but the magnitude of GFR loss was more important at higher GFR (higher dispersion of circles) than at lower GFR values. Fifty-five percent of participants ($n=47$) classified as stage 1 at baseline worsened to stage 2 and 10% ($n=9$) worsened to stage 3 at follow-up. However 57% of people with stage 2 and 83% with stage 3 at baseline stayed in the same class of CKD at follow-up and 39% of people with stage 2 and 6% of participants with stage 3 at baseline worsened by one stage. Five percent of the study population displayed an improvement of their KF at follow-up. The magnitude of improvement was larger at higher KF (GFR > 90 mL/min).

Figure 3B shows the delta value versus GFR estimation at baseline. People with a higher level of KF at baseline experienced a larger magnitude of GFR loss (line's steep slope) compared to those with lower level of KF. Persons with GFR < 60 mL/min at baseline experienced less variation of

their KF as shown by the quadratic regression curve (curve with 95% confidence interval) which was associated with a statistically significant better fit (adjusted $R^2=10.4\%$) than a linear regression (adjusted $R^2=9.6\%$) (likelihood ratio test, $p=0.0093$).

Table 2 shows the crude and final adjusted odds ratio of having a GFR < 60 mL/min at 3 years of follow-up among the whole population. In the univariate analyses, an age of 75 years and older, higher serum creatinine, a GFR < 60 mL/min at baseline, poor physical performance, two or more comorbidities, and SBP of 160 mmHg or higher were associated with a GFR < 60 mL/min at follow-up. Male gender, higher scores of MMSE, education, and BMI were associated with a significant protective effect.

In the final multivariate model, an age of 75 years and older, higher serum creatinine, a GFR < 60 mL/min at baseline and a SBP of 160 mmHg and higher were associated with a GFR < 60 mL/min at follow-up whereas male gender, former and current treatment for high blood pressure, and higher BMI were associated with a significant protective effect.

Discussion

Overall, these results highlight different points. Older patients do not represent a homogeneous population with a constant and irreversible loss of GFR throughout time. Different trajectories can be expected, including improvement of KF. They also stress the pitfall of relying only on serum creatinine as evidence of KF: only 19% of participants with GFR < 60 mL/min at baseline had an abnormal high level of serum creatinine.

In this cohort, participants with a criterion of CKD at baseline represented the most stable subset of the popula-

FIG. 3. (A) Glomerular filtration rate (GFR) estimation at 3 years of follow-up (FU) (y axis) according to GFR estimation at baseline (BL) (x axis) using the Cockcroft–Gault equation. (B) Yearly difference of renal function between baseline and follow-up, named Delta GFR versus glomerular filtration rate (GFR) estimation at baseline using the Cockcroft–Gault equation. A quadratic fit curve ($\text{delta GFR} = -1.8325 + 0.0463 \cdot \text{GFR} - 0.0008 \cdot \text{GFR}^2$) with its 95% confidence interval is also shown.

TABLE 2. ODDS RATIOS FOR GLOMERULAR FILTRATION RATE (GFR) LESS THAN 60 mL/MIN AT 3 YEARS OF FOLLOW-UP IN A POPULATION OF PEOPLE AGED 65 AND OLDER USING UNIVARIATE (ONE INDEPENDENT VARIABLE AT A TIME) AND MULTIVARIATE (ALL VARIABLES INCLUDED SIMULTANEOUSLY) LOGISTIC REGRESSION MODELS

Marker at baseline	Crude			Adjusted full model		
	OR	95% CI	p	OR	95% CI	p
Age, years						
<70	Reference			Reference		
70–74	1.44	[0.98–2.12]	0.061	1.20	[0.75–1.93]	0.438
75–79	6.21	[3.92–9.86]	<0.001	5.68	[3.13–10.30]	<0.001
≥80	15.26	[7.25–32.13]	<0.001	8.25	[3.14–21.64]	<0.001
Sex, males	0.56	[0.41–0.76]	<0.001	0.22	[0.13–0.39]	<0.001
Serum creatinine, mg/dL	14.74	[5.60–38.84]	<0.001	145.74	[25.59–829.95]	<0.001
GFR <60 mL/min, Cockcroft–Gault	16.85	[10.50–27.06]	<0.001	3.35	[1.78–6.30]	<0.001
Mini Mental State Examination, score	0.89	[0.84–0.94]	0.001	1.00	[0.91–1.09]	0.946
Education, years of school	0.92	[0.88–0.97]	0.002	0.95	[0.88–1.02]	0.139
Short Physical Performance Battery: poor performers	1.94	[1.29–2.92]	<0.001	0.92	[0.51–1.66]	0.777
Co-morbidities						
0	Reference			Reference		
1	1.36	[0.95–1.95]	0.091	1.46	[0.90–2.37]	0.125
≥2	1.64	[1.11–2.41]	0.013	1.63	[0.92–2.87]	0.093
SBP, mmHg						
<140	Reference			Reference		
140–149	1.25	[0.79–1.95]	0.337	1.52	[0.84–2.73]	0.163
150–159	1.00	[0.62–1.61]	0.998	1.22	[0.65–2.30]	0.537
≥160	1.83	[1.22–2.75]	0.003	2.31	[1.34–3.98]	0.003
Treatment for high blood pressure	0.84	[0.61–1.14]	0.265	0.53	[0.34–0.83]	0.005
Diabetes mellitus	0.92	[0.60–1.43]	0.727	1.00	[0.53–1.88]	0.998
Body mass index ^a	0.85	[0.82–0.89]	<0.001	0.83	[0.78–0.89]	<0.001
Stroke	0.86	[0.43–1.69]	0.658	–	–	–
Ischemic cardiomyopathy	1.14	[0.69–1.90]	0.604	–	–	–
Peripheral arterial disease	1.27	[0.83–1.94]	0.265	–	–	–

^aBody mass index (BMI) was treated as a continuous variable after having tested its log linearity relationship with the outcome. Abbreviations: OR, Odds ratio; CI, confidence interval; GFR, glomerular filtration rate; SBP, systolic blood pressure.

tion, whereas participants with a GFR ≥ 60 mL/min displayed larger variations of their GFR.

The overall mean change of GFR in our community-dwelling participants was -2.7 ± 0.2 mL/min per year. A smaller prospective study of 269 individuals over 65 years and living in the community of San Paulo found a similar overall change in GFR of -2.37 ± 0.23 mL/min per year using CG. A higher rate of GFR loss was also found in participants with higher levels of creatinine clearance at baseline, but interestingly at an older age.³¹ We would expect that older patients would have the lowest GFR. Indeed, in our study, older participants were more likely to be in sub-group LL, which displayed the lowest rate of GFR loss.

In a prospective study of a nonrepresentative Canadian population referred to a laboratory service comparing diabetic with nondiabetic participants over 66 years and followed during 2 years, the greatest decline in GFR as assessed with MDRD was found in diabetic subjects (-5.1 mL/min per 1.73 m^2 for diabetic men and -4.2 mL/min per 1.73 m^2 for diabetic women; -2.7 mL/min per 1.73 m^2 for men and -1.5 mL/min per 1.73 m^2 for women without diabetes). In this study, the proportion of people with a loss of KF over $15 \text{ mL/min per } 1.73 \text{ m}^2$ was greater for participants with

higher mean GFR over 2 years (13.6 % of subjects with mean GFR 60–89 mL/min per 1.73 m^2) compared to those with lower mean GFR (8.6% of subjects with mean GFR < 30 mL/min per 1.73 m^2). The authors decided to stratify the CKD stages by the mean of GFR along the entire period to reduce effect of regression to the mean phenomenon. This method is theoretically interesting but not relevant in clinical practice.³²

In our study, up to 10.4% of participants with GFR < 60 mL/min improved their KF at 3 years, results supporting that the natural history of KF is not always a progressive and irreversible decline with age. In the Baltimore longitudinal study of aging, 35% of all subjects had no absolute decrease in KF and around 1.6% showed a statistically significant increase in creatinine clearance with age.¹⁴ In the Cardiovascular Health Study using two measurements of kidney function, 39% of the cohort displayed an increase of their KF.³³

The strengths of the current study are that it uses data from a sample of community-dwelling older adults well characterized in terms of disease status and body composition. However, it represents a healthier subset of the population because it consists of older adults who survived for 3 years, consented to blood draws at both time points, and displayed mostly moderate KF impairment. Given that, the

rate of decline in KF may be underestimated, especially in the subset of the population with severe CKD. However, this survival bias probably may have a low impact on the results because no participants died due to advanced chronic kidney disease. Another limitation is that this study uses a single serum creatinine measurement at baseline and follow-up, therefore variability due to acute renal insufficiency can not be excluded. The urinary albumin-to-creatinine ratio was not assessed in this population and may have improved the predictive model of having a CKD at follow-up (Table 2), as it has been recently shown.^{34,35} There is no gold standard marker of KF leading to use an estimation equation of GFR not validated in an older population. Finally, results regarding kidney function evolution may be partly explained by a regression-to-the mean phenomenon, especially regarding the larger drop of GFR among participants with a $\text{GFR} \geq 60 \text{ mL/min}$ at baseline in the first group. However, the fact that the mean delta in the whole population is negative underlines that there is a clear, but not homogeneous, decline of kidney function with age.

In our study, using the MDRD equation, only 10% of the included subjects had a $\text{GFR} < 60 \text{ mL/min}$ per 1.73 m^2 at baseline compared to 33% using CG. Overestimation of the true GFR by the MDRD equation may explain an important classification difference at baseline, leading to missing an important subset of the population displaying a GFR around the cut-off values for CKD (60 mL/min). However, using either MDRD or CG, patients displaying criteria of CKD at baseline represented the more stable population.

After adjusting CG to BSA, 67 subjects out of 676 (9.9%) were classified differently at baseline from results obtained with CG: 26 were found to have a worse KF and conversely 41 were found to have a better KF at baseline.³³ Without a gold standard marker of KF, we can not tell which classification is closer to reality. None of these equations is validated in this extreme age group, therefore we decided to keep CG for all our analyses because it is the most used estimation equation in the geriatric clinical setting. These data also stress the need to develop an equation specific to the very old population.

In a community-based longitudinal study of adults over 65 belonging to The Cardiovascular Health Study, mean annual GFR decline was assessed using MDRD. In this study, older age and female gender were predictors of annual KF decline.³³ We found similar results. In addition, in our study, higher SBP was also found to be a predictor of loss of KF, a finding corroborated by others^{36,37} and thus stressing the role of screening and management of cardiovascular risk factor in slowing rate loss of KF. Gender effect regarding progression of KF remains controversial; while some studies have found a protective effect,³³ others have found that male gender was predictor of KF decline.^{37, 38}

In our study, diabetes did not affect subgroup allocation (Table 1) or CKD at follow-up risk (Table 2) and may reflect that diabetic nephropathy is not the major determinant of CKD impairment in an older population and that CKD evolution may be explained by other causes such as nephrosclerosis due to higher SBP. This hypothesis was also suggested in another study assessing older hospitalized diabetic patients in which renal insufficiency was found to often occur without albuminuria, an early-stage marker of diabetic glomerulopathy.³⁹

To assess the long-term prognosis and change in GFR of patient with criteria of CKD, a longitudinal observation study of people living in northern Norway, referred for laboratory testing and displaying GFR between 30 and 59 mL/min per 1.73 m^2 using MDRD found a 10-year cumulative incidence of renal failure as low as 0.04 (95% CI 0.03–0.06). However, 10-year cumulative incident mortality reached up to 0.51 (95% CI 0.48–0.55). Causes of death were not identified, but renal failure was excluded as a cause based on expected GFR at the time of death. In this population, a similar mean change in GFR was found (-1.04 mL/min per 1.73 m^2 per year; -1.60 mL/min per 1.73 m^2 per year for subjects aged 70–79 years, respectively, >79 years). The authors conclude that high mortality pre-empted the development of renal failure in many patients.³⁸

The same pattern was found in a large national cohort of U.S. veterans who met criteria for stage 3 or higher CKD. Older participants, especially those aged 75 years and older, were far more likely to die than to develop end-stage renal disease (ESRD). In this cohort, the threshold of GFR estimated using MDRD, and below which the risk of ESRD exceeds the risk of death, varied by age and was below 15 mL/min per 1.73 m^2 for those aged 65–84 years old. For participants aged 85 years and older, the risk of death always exceeds the risk of ESRD.⁴⁰ The association of all-cause and cardiovascular mortality with CKD was assessed in a large cohort study of people over 75 years, with a mean GFR of 62.4 mL/min per 1.73 m^2 for men and 55.8 mL/min per 1.73 m^2 for women, registered in 53 general practices in Great Britain, with a median follow-up of 7.3 years. In this community-dwelling older population, results showed a graded and independent increase in all-cause and cardiovascular mortality risk as GFR decreased, especially in men and those with a $\text{GFR} \leq 45 \text{ mL/min}$ per 1.73 m^2 .⁴¹ The same pattern was found in a longitudinal study of adult members of a Health Maintenance Organization in Oregon in which death was far more common than dialysis in all stages. Further analysis found that CHF, coronary artery disease, diabetes, and anemia were more prevalent in the patients who died, stressing the need to screen and manage CKD complications in this population.⁴²

In conclusion, this study demonstrates that older people with impaired renal function represent a subset of the population with a very low progression of renal disease and therefore are at higher risk to suffer from co-morbidities related to CKD than to progress to end-stage renal disease.

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Author Disclosure Statement

No competing financial interests exist.

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(Appendix follows→)

Appendix

Equation 1: CG formula²⁸:

$$\text{GFR (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times (0.85 \text{ if } \text{♀})}{72 \times \text{creatinine (mg /dL)}}$$

Equation 2: MDRD formula²⁹:

$$\text{GFR (mL /min per } 1.73\text{m}^2) = 186 \times (\text{creatinine (mg /dL)})^{-1.154} \times [\text{age (years)}]^{-0.203} \times (0.742 \text{ if } \text{♀})$$

Because the studied population was Italian, we did not have to adjust this equation for race.

Equation 3: CG adjusted to body surface area (BSA) according to the Dubois and Dubois formula³⁰:

$$\begin{aligned} \text{GFR (mL /min per } 1.73\text{m}^2) &= \text{CG} \times [1.73/\text{BSA}] \\ \text{BSA (m}^2) &= 0.20247 \times \text{Height (m)}^{0.725} \times \text{Weight (kg)}^{0.425} \end{aligned}$$