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Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

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ABSTRACT

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BACKGROUND

End-stage renal disease substantially increases the risks of death, cardiovascular disease, and use of specialized health care, but the effects of less severe kidney dysfunction on these outcomes are less well defined.

METHODS

We estimated the longitudinal glomerular filtration rate (GFR) among 1,120,295 adults within a large, integrated system of health care delivery in whom serum creatinine had been measured between 1996 and 2000 and who had not undergone dialysis or kidney transplantation. We examined the multivariable association between the estimated GFR and the risks of death, cardiovascular events, and hospitalization.

RESULTS

The median follow-up was 2.84 years, the mean age was 52 years, and 55 percent of the group were women. After adjustment, the risk of death increased as the GFR decreased below 60 ml per minute per 1.73 m² of body-surface area: the adjusted hazard ratio for death was 1.2 with an estimated GFR of 45 to 59 ml per minute per 1.73 m² (95 percent confidence interval, 1.1 to 1.2), 1.8 with an estimated GFR of 30 to 44 ml per minute per 1.73 m² (95 percent confidence interval, 1.7 to 1.9), 3.2 with an estimated GFR of 15 to 29 ml per minute per 1.73 m² (95 percent confidence interval, 3.1 to 3.4), and 5.9 with an estimated GFR of less than 15 ml per minute per 1.73 m² (95 percent confidence interval, 5.4 to 6.5). The adjusted hazard ratio for cardiovascular events also increased inversely with the estimated GFR: 1.4 (95 percent confidence interval, 1.4 to 1.5), 2.0 (95 percent confidence interval, 1.9 to 2.1), 2.8 (95 percent confidence interval, 2.6 to 2.9), and 3.4 (95 percent confidence interval, 3.1 to 3.8), respectively. The adjusted risk of hospitalization with a reduced estimated GFR followed a similar pattern.

CONCLUSIONS

An independent, graded association was observed between a reduced estimated GFR and the risk of death, cardiovascular events, and hospitalization in a large, community-based population. These findings highlight the clinical and public health importance of chronic renal insufficiency.

MORE THAN 400,000 AMERICANS have end-stage renal disease, and over 300,000 of these patients require maintenance dialysis.[1] Mortality rates remain above 20 percent per year with the use of dialysis, with more than half of the deaths related to cardiovascular disease. The annual direct medical costs for end-stage renal disease are nearly $23 billion.[1] Although an estimated 8 million adults in the United States have chronic kidney disease of at least stage 3 (as defined by an estimated glomerular filtration rate [GFR] of less than 60 ml per minute per 1.73 m² of body-surface area),[2] less is known about the rates of death, cardiovascular disease, and resource use among persons with a reduced estimated GFR who are not yet receiving maintenance dialysis.

Several, but not all, previous studies suggested that mild-to-moderate elevations in serum creatinine levels are associated with increased rates of death from any cause[3-9] and from cardiovascular causes,[5,7,10-13] but whether chronic kidney disease independently increases the risk of any type of cardiovascular disease has not been established.[4-7,14] Furthermore, previous studies have been limited by the inclusion of relatively small numbers of persons with kidney disease,[3-8,11-17] the use of dichotomous groups of estimated kidney function,[3-8,15] the use of the serum creatinine level alone as a proxy for GFR and nonuniform cutoff values to define kidney disease,[3-11,15] lack of information on longitudinal changes in GFR and coexisting conditions,[3-11,14-17] selected populations,[6,8,11,14,16] and populations with limited racial or ethnic diversity. In addition, few studies have investigated the association between chronic kidney disease and the risk of hospitalization,[18] which has important economic implications.

Using longitudinal measures of estimated GFR, a more accurate method of assessing kidney function than the measurement of serum creatinine alone, we examined the effect of the severity of kidney dysfunction on the risks of death, cardiovascular events, and hospitalization among a large, diverse group of adults. We hypothesized that there would be a graded, independent association between the estimated GFR and the risks of these outcomes.

METHODS

STUDY SAMPLE AND MEASURES OF KIDNEY FUNCTION

The Kaiser Permanente Renal Registry included all adult members (20 years of age or older) of Kaiser Permanente of Northern California, a large integrated health care system insuring more than 35 percent of the adult population of the San Francisco Bay Area, whose kidney function was known. To be eligible for the registry, the subjects had to have had one or more outpatient determinations of serum creatinine levels recorded in a health-plan laboratory database between January 1, 1996, and December 31, 2000. We excluded subjects who had already received a kidney transplant or who were receiving maintenance dialysis at entry. Given the nature of the study, the institutional review board of the Kaiser Foundation Research Institute determined that informed consent was not required.

We used the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate the GFR.[19,20] We calibrated the measurement of serum creatinine by the Kaiser regional laboratory against that of the MDRD core laboratory.[21] The date of the first measurement of GFR during the study period was considered the subject's index date (baseline). Changes in GFR during follow-up were estimated from serum creatinine determinations not associated with hospitalizations to reflect more accurately stable estimates of kidney function. We used a modified National Kidney Foundation classification of chronic kidney disease,[22] which classifies estimated GFR in the following ranges: at least 60 ml per minute per 1.73 m², 45 to 59 ml per minute per 1.73 m² (stage 3a), 30 to 44 ml per minute per 1.73 m² (stage 3b), 15 to 29 ml per minute per 1.73 m² (stage 4), and less than 15 ml per minute per 1.73 m² (stage 5).

CHARACTERISTICS OF THE SUBJECTS

Data on age, sex, and racial or ethnic group were obtained from health-plan databases. All names and identifiers were removed before any data were analyzed, according to procedures approved by the institutional review board at Kaiser.

We identified coexisting illnesses using validated methods[23-26] based on health-plan databases for hospitalization-discharge diagnoses, ambulatory diagnoses, laboratory results, and medication prescriptions, as well as regional cancer-registry data[24] (diagnostic criteria are listed in the Appendix). These diagnoses included coronary disease, stroke or transient ischemic attack, heart failure, peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, lung or liver disease, cancer, and dementia. We also evaluated laboratory-database entries for serum albumin to identify subjects with a value of 3.5 g per deciliter or less. The pres-

ence of proteinuria was based on laboratory-database entries of urine dipstick results of 1+ or greater (approximately 30 mg per deciliter or greater) in the absence of a possible urinary tract infection (i.e., concomitant positive test for urinary nitrite or esterase).

Socioeconomic status was assigned with the use of 2000 U.S. Census-block data, which generally correspond to city blocks or neighborhoods.[28] Subjects with a low income were defined as those living in a Census-block group with a median annual household income under $35,000, and those with a low level of education were categorized as those living in a Census-block group in which more than 25 percent of residents older than 25 years had less than a 12th-grade education.

OUTCOMES

Data on subjects were censored if they underwent kidney transplantation or disenrolled from the health plan, which was defined as a continuous gap in membership of more than 90 days without the interim use of services. Incident end-stage renal disease, defined by the receipt of maintenance dialysis or a kidney transplant, was identified from a comprehensive health-plan registry.[29] The primary outcomes of interest included death from any cause, cardiovascular events, and hospitalizations through December 31, 2000. Death was identified from a search of health-plan databases and the California death registry.[30] A cardiovascular event was defined as hospitalization for coronary disease, heart failure, stroke, or peripheral arterial disease (see the Appendix).

STATISTICAL ANALYSIS

Event rates were directly adjusted for age with the use of the age distribution of the adult source population and are presented as the number of events per 100 person-years, with 95 percent confidence intervals. To evaluate the independent effect of the estimated GFR on outcomes, we used Cox proportional-hazards models with time-dependent covariates for changing GFR and coexisting illnesses. All variables known to be associated with either the estimated GFR or the outcomes were included in the final models, along with any variables associated with a reduced estimated GFR (i.e., less than 60 ml per minute per 1.73 m²) in univariate analyses with a P value of less than 0.01. Age was entered as a categorical variable (20 to 49, 50 to 59, 60 to 69, 70 to 79, and 80 years or older), with other co-

variates included as dichotomous variables. For recurrent outcomes of cardiovascular events and hospitalizations, we used a "sandwich" estimate of the variance–covariance matrix to obtain standard errors accommodating the clustering of observations on subjects.[31] In the model for death, we did not include cardiovascular events or hospitalizations that occurred after the index date, since they were hypothesized to be part of the pathway by which reduced GFR may increase the risk of death.

Each subject and time was assigned an estimated GFR with the use of the last-value-carried-forward method. Given the varying numbers and spacing of measurements of GFR for each subject, this approach may preferentially attribute outcome events to higher levels of GFR. To address this possibility we analyzed a subgroup of subjects who had had regular serum creatinine determinations spaced between 1 and 14 months apart throughout follow-up. Also, although age and sex are important predictors of adverse events and are incorporated into the MDRD equation, we found no interactions among age, sex, and GFR and thus present only the main-model results.

All analyses were conducted with the use of SAS software (version 8.2). The institutional review board of each collaborating institution approved the study.

RESULTS

BASELINE CHARACTERISTICS

We identified 1,120,295 adults who had had one or more outpatient measurements of serum creatinine, had not previously received dialysis or a kidney transplant, and were alive on the index date. The median number of outpatient measurements of serum creatinine per subject during follow-up was three (interquartile range, one to four).

Subjects with a low estimated GFR at baseline were older than those with an estimated GFR of at least 60 ml per minute per 1.73 m², and there was greater minority-group representation among subjects with a low estimated GFR (Table 1). As compared with the group with an estimated GFR of at least 60 ml per minute per 1.73 m², the groups with a reduced estimated GFR also had a higher prevalence of prior cardiovascular disease, proteinuria, diabetes, hypertension, a serum albumin level of 3.5 g per deciliter or less, prior hospitalizations, and other coexisting illnesses (Table 1). Among the 60.7 percent of subjects who had one or more urine

Table 1. Baseline Characteristics of 1,120,295 Ambulatory Adults, According to the Estimated GFR at Baseline.*

Characteristic	Total Cohort (N=1,120,295)	Estimated GFR at Baseline				
		≥60 ml/min/1.73 m² (N=924,136)	45–59 ml/min/1.73 m² (N=153,426)	30–44 ml/min/1.73 m² (N=34,275)	15–29 ml/min/1.73 m² (N=7085)	<15 ml/min/1.73 m² without dialysis (N=1373)
Age (yr)	52.2±16.3	49.1±15.1	65.4±13.5	71.2±12.9	70.1±14.5	63.0±16.1
Female sex (%)	54.6	53.4	60.7	61.6	57.7	50.6
Race or ethnic group (%)†						
White	50.9	47.2	68.4	71.4	66.3	54.9
Black	7.4	7.2	4.7	6.7	10.6	16.8
Hispanic	5.9	6.3	3.9	3.9	5.4	6.8
Asian	8.1	8.5	6.4	6.3	7.6	11.9
Pacific Islander	0.04	0.03	0.03	0.1	0.2	0.4
Native American	0.5	0.5	0.5	0.6	0.7	0.7
Mixed or nonblack	2.4	2.4	2.2	2.9	4.0	4.5
Other or unknown	24.8	27.4	13.9	8.0	5.3	4.2
Medical history (%)						
Coronary heart disease	6.3	4.5	13.2	20.6	24.5	17.9
Stroke or transient ischemic attack	2.6	1.7	5.7	10.2	12.8	10.2
Peripheral arterial disease	1.8	1.1	3.9	8.2	12.0	8.9
Chronic heart failure	2.1	1.0	5.2	12.6	20.8	18.5
Known proteinuria	6.3	5.1	8.9	17.7	33.7	50.2
Diabetes mellitus	9.6	8.6	12.3	19.6	28.2	31.1
Diagnosed hypertension	19.1	15.4	33.7	45.8	49.6	50.3
Dyslipidemia	27.9	26.8	33.4	30.9	29.3	28.0
Chronic lung disease	19.1	18.6	21.2	22.4	20.7	19.1
Chronic liver disease	0.2	0.2	0.3	0.6	0.9	1.4
Cancer	2.9	2.5	4.6	5.5	5.7	5.8
Serum albumin ≤3.5 g/dl	1.7	1.2	2.8	5.9	13.7	24.0
Diagnosed dementia	0.8	0.5	1.9	3.2	4.0	3.1
Prior hospitalizations	22.4	20.3	29.4	41.2	50.4	51.1

* Plus–minus values are means ±SD. Because of rounding, percentages may not total 100.
† Information on race and ethnic group was reported by the subjects; information was not available for 5.3 percent of the subjects.

dipstick determinations at any time during follow-up, 17.6 percent were found to have proteinuria. Among the 21.2 percent of subjects who had one or more serum albumin determinations at any time during follow-up, 27.8 percent were found to have reduced levels.

OUTCOMES ACCORDING TO THE ESTIMATED GFR

The median follow-up among the 1,120,295 subjects was 2.84 years (interquartile range, 1.65 to 4.01), which amounts to 3,132,192 person-years. Overall, 21.8 percent of subjects disenrolled during follow-up, but those who disenrolled were substantially younger, were relatively unlikely to have a reduced estimated GFR, and had fewer coexisting illnesses than those who remained enrolled (data not shown). The vital status was complete for all subjects.

During follow-up, 3171 (0.28 percent) subjects began maintenance dialysis and 329 (0.03 percent) underwent kidney transplantation. There were 51,424 deaths, 138,291 cardiovascular events, and 554,651 hospitalizations. Age-standardized rates of death, cardiovascular events, and hospitalization increased substantially with progressively lower estimated GFRs (Fig. 1).

The group of subjects with an estimated GFR of at least 60 ml per minute per 1.73 m² was used as the reference group in the analysis of the association between the level of the estimated GFR and each outcome. After adjustment for differences in sociodemographic characteristics and the presence or absence of prior cardiovascular disease, prior hospitalizations, diabetes, hypertension, dyslipidemia, lung or liver disease, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, proteinuria, and the initiation of dialysis during follow-up, the risk of death from any cause increased sharply as the estimated GFR declined, ranging from a 17 percent increase in risk with an estimated GFR of 45 to 59 ml per minute per 1.73 m² to

a nearly 600 percent increase with an estimated GFR of less than 15 ml per minute per 1.73 m² (Table 2). The adjusted risk of any cardiovascular event also increased as the estimated GFR decreased, ranging from a 43 percent increase in risk with an estimat-

Figure 1. Age-Standardized Rates of Death from Any Cause (Panel A), Cardiovascular Events (Panel B), and Hospitalization (Panel C), According to the Estimated GFR among 1,120,295 Ambulatory Adults.

A cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease. Error bars represent 95 percent confidence intervals. The rate of events is listed above each bar.
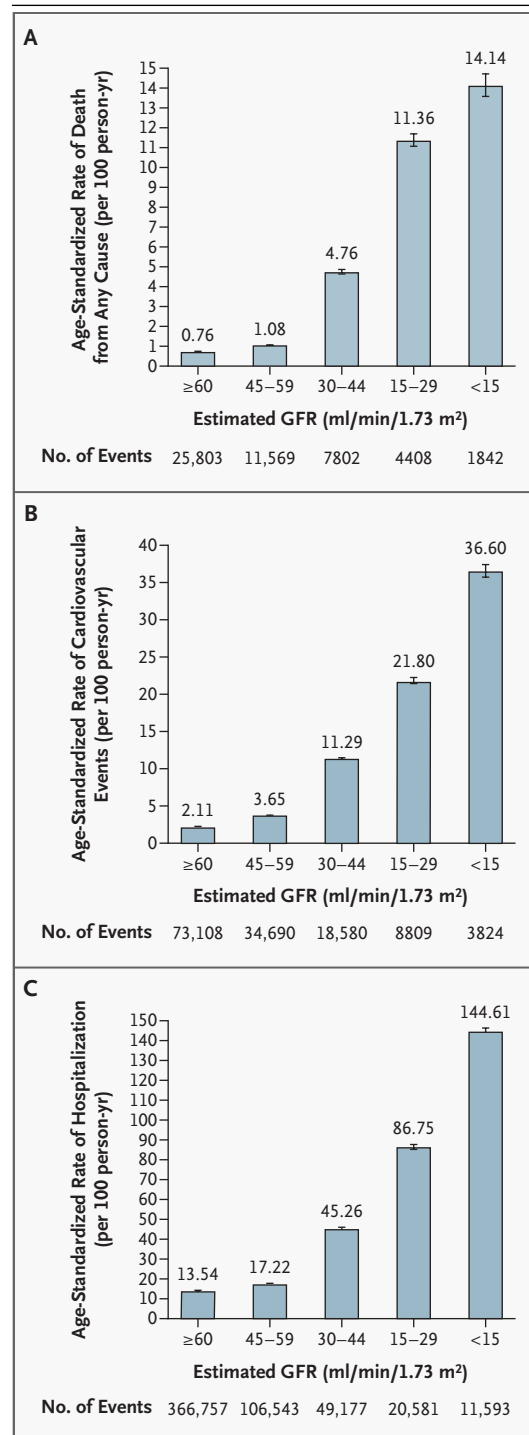
ed GFR of 45 to 59 ml per minute per 1.73 m² to a 343 percent increase with an estimated GFR of less than 15 ml per minute per 1.73 m² (Table 2). Finally, the adjusted risk of hospitalization increased as the estimated GFR decreased, ranging from an increase of 14 percent with an estimated GFR of 45 to 59 ml per minute per 1.73 m² to an increase of 315 percent with an estimated GFR of less than 15 ml per minute per 1.73 m² (Table 2). The presence of documented proteinuria was also an independent predictor of death (adjusted hazard ratio, 1.3; 95 percent confidence interval, 1.3 to 1.4), cardiovascular events (adjusted hazard ratio, 1.3; 95 percent confidence interval, 1.2 to 1.3), and hospitalization (adjusted hazard ratio, 1.4; 95 percent confidence interval, 1.4 to 1.4).

In a subgroup of 172,144 subjects who had regular measurements of serum creatinine during follow-up (mean [±SD] number of measurements, 3.3±2.1; mean interval between measurements, 7.5±3.4 months), the adjusted risks of adverse outcomes differed materially from those for the entire cohort only among the subjects with an estimated GFR of 45 to 59 ml per minute per 1.73 m². In the analysis of the subgroup itself, as compared with the subjects with an estimated GFR of at least 60 ml per minute per 1.73 m², the subjects with an estimated GFR of 45 to 59 ml per minute per 1.73 m² had a similar adjusted hazard ratio for death (1.0; 95 percent confidence interval, 1.0 to 1.1) and hospitalization (1.0; 95 percent confidence interval, 1.0 to 1.0). The adjusted risk of cardiovascular events was also attenuated (1.2; 95 percent confidence interval, 1.1 to 1.3).

DISCUSSION

Among a large, diverse population of adults, a reduced estimated GFR was associated with increased risks of death, cardiovascular events, and hospitalization that were independent of known risk factors, a history of cardiovascular disease, and the presence of documented proteinuria. Our study demonstrates that these graded risks of adverse events rose sharply for subjects with an estimated GFR of less than 45 ml per minute per 1.73 m² for each outcome examined both in the overall cohort and in subgroup analyses. Furthermore, in the cohort as a whole, the absolute rates of these outcomes were considerably higher than the risk of end-stage renal disease.

There has been rapidly growing interest in the

Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.*

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	adjusted hazard ratio (95 percent confidence interval)		
≥60 ml/min/1.73 m²†	1.00	1.00	1.00
45–59 ml/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

* The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.
† This group served as the reference group.

relation between kidney disease and the risk of death and cardiovascular disease. With recognition that the presence of chronic kidney disease that does not necessitate dialysis is of considerable importance, several studies have examined the association of different cutoff values of serum creatinine with the risks of death from any cause, death from cardiovascular causes, and cardiovascular events, and most,[3,4,6-12,15] but not all,[5,13] of these studies have found increased risks with higher serum creatinine levels. Others have noted high rates of hospitalization among persons with elevated serum creatinine levels.[18] However, since serum creatinine levels are not linearly associated with GFR,[32] the use of predictive equations (the Cockcroft–Gault equation for creatinine clearance[33] and the MDRD equation for estimated GFR[19]) has been proposed as a more accurate means of estimating the GFR, with the MDRD equation having better predictive ability in certain populations.[20]

Relatively few studies have evaluated the estimated GFR and the risk of outcomes in the general population. In the Second National Health and Nutrition Examination Survey (NHANES II),[12] an estimated GFR of less than 70 ml per minute per 1.73 m² was associated with a 68 percent increase in the risk of death from any cause and a 51 percent increase in the risk of death from cardiovascular causes, as compared with an estimated GFR of at least 90 ml per minute per 1.73 m². In the Athero-

sclerosis Risk in Communities Study,[17] an estimated GFR of 15 to 59 ml per minute per 1.73 m² at baseline was associated with a 38 percent increase in the risk of cardiovascular disease, as compared with an estimated GFR of 90 to 150 ml per minute per 1.73 m². Similar results were obtained in a cohort of older adults (at least 65 years of age)[16] for an estimated GFR of 15 to 59 ml per minute per 1.73 m², as compared with an estimated GFR of 90 to 130 ml per minute per 1.73 m². However, the NHANES I Epidemiologic Follow-up Study did not find a significant association between an estimated GFR of approximately 30 to 60 ml per minute per 1.73 m² and the risk of death from any cause or death from cardiovascular causes.[13] In addition, in the Framingham Heart Study, an elevated serum creatinine level — 1.5 to 3.0 mg per deciliter (133 to 265 μmol per liter) in men and 1.4 to 3.0 mg per deciliter (124 to 265 μmol per liter) in women — was associated with a significant risk of death among men but not women and was not associated with the risk of cardiovascular events in either sex.[5]

These studies were limited by the use of a single measurement of kidney function, the use of a broad range of definitions of diminished kidney function, and the inclusion of relatively small numbers of persons with kidney disease, thus limiting their statistical power to examine different levels of reduced GFR. Furthermore, although several studies used the MDRD equation to estimate GFR, serum creatinine measurements were not directly calibrated to the values of the MDRD laboratory, so the absolute threshold level of GFR associated with adverse outcomes cannot be known with confidence.

Our study further delineates the relation between the GFR and the risk of adverse events. We found nonlinear relations between the GFR and the risks of death, cardiovascular events, and hospitalization, with an increased risk associated with an estimated GFR of less than 60 ml per minute per 1.73 m², which further rose sharply when values dropped below 45 ml per minute per 1.73 m². We found that an estimated GFR of 15 to 29 ml per minute per 1.73 m² and an estimated GFR of less than 15 ml per minute per 1.73 m² in the absence of dialysis were associated with strikingly high age-adjusted mortality rates (11.4 and 14.1 per 100 person-years, respectively). These rates approach the rates among patients with treated end-stage renal disease.[1] Although the prevention of end-stage renal disease remains a very important goal in patients with kidney disease, more effective interven-

tions are clearly needed to reduce the disproportionate cardiovascular and economic burden in this population.

Multiple possible explanations exist for the association between chronic kidney disease and increased risks of death and cardiovascular disease. We observed an increased prevalence of prior cardiovascular disease, known risk factors for cardiovascular events and death, and coexisting conditions with lower levels of the estimated GFR. However, a reduced estimated GFR was an independent and strong risk factor for adverse outcomes. Reduced kidney function is also associated with increased levels of inflammatory factors,[34,35] abnormal apolipoprotein levels,[34] elevated plasma homocysteine,[34] enhanced coagulability,[35] anemia,[36] left ventricular hypertrophy,[37] increased arterial calcification,[38] endothelial dysfunction,[39] and arterial stiffness.[40] Whether and how these and other factors interact to increase the risk of adverse outcomes remains unclear but are the focus of ongoing investigations.[41] Our large, ethnically diverse population is typical of patients receiving usual clinical care rather than referral populations, recruited cohorts, or clinical-trial participants, and thus, our results are probably more generalizable. The inclusion of large numbers of subjects with a spectrum of kidney disease also enabled us to make a more detailed evaluation of the effect of the level of the GFR on outcomes. Use of outpatient serum creatinine values that were directly calibrated to those of the MDRD core laboratory increased our confidence in the validity of the observed associations of absolute, not just relative, levels of the estimated GFR. Most subjects had serial estimates of the GFR in order to characterize kidney function over time as accurately as possible. We had complete records of deaths and hospitalizations among these subjects that occurred at health-plan and other facilities. Our study also shows that the use of a baseline estimate of the GFR alone may lead to the misattribution of events to a certain level of GFR measured in the distant past and to the subsequent attenuation of the true strength of the association between a reduced GFR and outcomes.

Our study had several limitations. As a study of subjects who received usual clinical care, estimates of the GFR were not available for the entire source population. For example, patients with a reduced GFR who did not use medical services would not have been included. However, over half of adult members of the health plan had serum creatinine

measurements, which allowed for a robust assessment of the estimated GFR and outcomes among more than 1.1 million subjects. We did not have information on tobacco or alcohol use, diet, physical activity, other possible unmeasured confounders (e.g., body-mass index), or the severity of certain conditions (e.g., level of blood pressure or severity of diabetes). Nevertheless, residual confounding is unlikely to explain the large effect estimates observed for most categories of a reduced estimated GFR. Finally, since our study was conducted among insured adults in northern California, our results may not be completely generalizable to uninsured persons or persons in other geographic regions.

In conclusion, we found an independent, graded association between lower levels of the estimated GFR and the risks of death, cardiovascular events, and hospitalization. These risks were evident at an estimated GFR of less than 60 ml per minute per 1.73 m² and substantially increased with an estimated GFR of less than 45 ml per minute per 1.73 m². Our findings support the validity of the National Kidney Foundation staging system for chronic kidney disease[22] but suggest that the system could be further refined, since all persons with stage 3 chronic kidney disease (GFR, 30 to 59 ml per minute per 1.73 m²) may not be at equal risk for each outcome. Our findings highlight the clinical and public health importance of chronic kidney disease that does not necessitate dialysis.

APPENDIX

The following criteria and *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM), and *Current Procedural Terminology* (CPT) codes, if relevant, were used to define coexisting illnesses.

Condition	Criteria	ICD-9-CM	CPT Code*
Acute myocardial infarction	Primary discharge diagnosis in hospitalization databases	410	NA
Unstable and stable angina	Primary discharge diagnosis in hospitalization databases or physician-assigned diagnosis in ambulatory-visit database	411, 413	NA
Coronary artery disease	Primary discharge diagnosis in hospitalization databases or physician-assigned diagnosis in ambulatory-visit database	414.0, 414.8, 414.9	NA
Percutaneous coronary intervention	Procedural code in hospitalization and ambulatory-visit databases	36.01–36.02, 36.05, 36.06, 36.09	92980–92981, 92982, 92984–92996
Coronary-artery bypass surgery	Procedural code in hospitalization databases	36.10–36.17, 36.19	33510–33519, 33521–33523, 33533–33536
Ischemic stroke	Primary discharge diagnosis in hospitalization databases or physician-assigned diagnosis in emergency-department database	433.x1, 434.x1, 436.0	NA
Transient ischemic attack	Primary discharge diagnosis in hospitalization databases or physician-assigned diagnosis in emergency-department database	435	NA
Chronic heart failure	Primary discharge diagnosis in hospitalization databases	398.91, 402.01, 402.11, 402.91, 428.0, 428.1, 428.9	NA
Peripheral arterial disease	Primary discharge diagnosis or procedural code in hospitalization databases or physician-assigned diagnosis in ambulatory-visit database	440.0–440.9, 38.13, 38.14, 38.15, 38.16, 38.18, 39.22, 39.24, 39.25, 39.26, 39.28	35450, 35452, 35454, 35456, 35458, 35459, 35470–35475, 35879, 75962, 75964, 75966, 75968, 33322, 33335, 33860, 33870, 35511, 35516, 35518, 35521, 35531, 35533, 35536, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35560, 35563, 35565, 35566, 35571, 35582, 35583, 35585, 35587, 35612, 35616, 35621, 35623, 35631, 35636, 35641, 35646, 35650, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671

Appendix (Continued).

Condition	Criteria	ICD-9-CM	CPT Code*
Diabetes mellitus	Validated health plan registry based on inpatient or outpatient diagnoses, antidiabetes therapies, laboratory results, and patient self-report[26]	See Selby et al.[26]	See Selby et al.[26]
Diagnosed hypertension	Two or more physician-assigned diagnoses in ambulatory-visit database or one outpatient diagnosis plus receipt of antihypertensive pharmacologic therapy found in pharmacy database	401–405	NA
Dyslipidemia	Physician-assigned clinical diagnosis in ambulatory database, record of filled prescriptions for lipid-lowering therapies in automated pharmacy databases within five years before index date, or lipid levels that met the cutoffs for elevated low-density lipoprotein and reduced high-density lipoprotein cholesterol identified in laboratory databases with the use of Adult Treatment Panel III guidelines[27]†	272.0, 272.2, 272.4	NA
Chronic lung disease	Primary discharge diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, or asthma in hospitalization databases or physician-assigned diagnosis in ambulatory-visit databases	491.x, 492.x, 493.x, 496, 518.1, 518.2	NA
Chronic liver disease	Primary discharge diagnosis of cirrhosis or chronic liver disease in hospitalization database or physician-assigned diagnosis in ambulatory-visit database	571	NA
Dementia	Physician-assigned diagnosis of dementia or organic brain disease found in ambulatory-visit database	290, 294, 331	NA
Cancer (other than localized, nonmelanoma skin cancer)	Comprehensive health-plan registry linked to regional Surveillance, Epidemiology, and End Results data[24]	See Fireman et al.[24]	See Fireman et al.[24]

* NA denotes not applicable.
† Subjects could have met any or all of the criteria.

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