ONLINE FIRST

Age and Association of Kidney Measures With Mortality and End-stage Renal Disease

Stein I. Hallan, MD, PhD
Kunihiro Matsushita, MD, PhD
Yingying Sang, MS
Bakhtawar K. Mahmoodi, MD, PhD
Corri Black, MBChB, MSc, FFPH
Areef Ishani, MD, MS
Nanne Kleefstra, MD, PhD
David Naimark, MD, MSc, FRCP(C)
Paul Roderick, MD, FRCP
Marcello Tonelli, MD, SM
Jack F. M. Wetzels, MD, PhD
Brad C. Astor, PhD, MPH
Ron T. Gansevoort, MD, PhD
Adeera Levin, MD
Chi-Pang Wen, MD, MPH, DrPH
Josef Coresh, MD, PhD
for the Chronic Kidney Disease Prognosis Consortium

Context Chronic kidney disease (CKD) is prevalent in older individuals, but the risk implications of low estimated glomerular filtration rate (eGFR) and high albuminuria across the full age range are controversial.

Objective To evaluate possible effect modification (interaction) by age of the association of eGFR and albuminuria with clinical risk, examining both relative and absolute risks.

Design, Setting, and Participants Individual-level meta-analysis including 2 051 244 participants from 33 general population or high-risk (of vascular disease) cohorts and 13 CKD cohorts from Asia, Australasia, Europe, and North/South America, conducted in 1972-2011 with a mean follow-up time of 5.8 years (range, 0-31 years).

Main Outcome Measures Hazard ratios (HRs) of mortality and end-stage renal disease (ESRD) according to eGFR and albuminuria were meta-analyzed across age categories after adjusting for sex, race, cardiovascular disease, diabetes, systolic blood pressure, cholesterol, body mass index, and smoking. Absolute risks were estimated using HRs and average incidence rates.

Results Mortality (112 325 deaths) and ESRD (8411 events) risks were higher at lower eGFR and higher albuminuria in every age category. In general and high-risk cohorts, relative mortality risk for reduced eGFR decreased with increasing age; eg, adjusted HRs at an eGFR of 45 mL/min/1.73 m^2 vs 80 mL/min/1.73 m^2 were 3.50 (95% CI, 2.55-4.81), 2.21 (95% CI, 2.02-2.41), 1.59 (95% CI, 1.42-1.77), and 1.35 (95% CI, 1.23-1.48) in age categories 18-54, 55-64, 65-74, and ≥75 years, respectively ($P<.05$ for age interaction). Absolute risk differences for the same comparisons were higher at older age (9.0 [95% CI, 6.0-12.8], 12.2 [95% CI, 10.3-14.3], 13.3 [95% CI, 9.0-18.6], and 27.2 [95% CI, 13.5-45.5] excess deaths per 1000 person-years, respectively). For increased albuminuria, reduction of relative risk with increasing age was less evident, while differences in absolute risk were higher in older age categories (7.5 [95% CI, 4.3-11.9], 12.2 [95% CI, 7.9-17.6], 22.7 [95% CI, 15.3-31.6], and 34.3 [95% CI, 19.5-52.4] excess deaths per 1000 person-years, respectively by age category, at an albumin-creatinine ratio of 300 mg/g vs 10 mg/g). In CKD cohorts, adjusted relative hazards of mortality did not decrease with age. In all cohorts, ESRD relative risks and absolute risk differences at lower eGFR or higher albuminuria were comparable across age categories.

Conclusions Both low eGFR and high albuminuria were independently associated with mortality and ESRD regardless of age across a wide range of populations. Mortality showed lower relative risk but higher absolute risk differences at older age.

JAMA. 2012;308(22):2349-2360
Published online October 30, 2012. doi:10.1001/jama.2012.16817 www.jama.com

CHRONIC KIDNEY DISEASE (CKD) is defined by reduced glomerular filtration rate (GFR <60 mL/min/1.73 m^2) or kidney damage (usually detected by high albuminuria; eg, ≥30 mg of albumin per 1 g of creatinine).[1] Chronic kidney disease affects 10% to 15% of adults in the United States, Europe, and Asia,[2-4] and the prevalence increases dramatically with age (from 4% at age 20-39 to 47% at age ≥70 years in the United States).[2]

Recently, it has been suggested that the definition and staging of CKD and corresponding clinical risk should be determined by the combination of estimated GFR (eGFR) and albuminuria levels.[5-7] These kidney measures are also used for cardiovascular risk stratification in clinical guidelines.[8,9] However, controversy exists about whether age modifies their independent and combined associations with clinical risk, partly because of different analytic approaches.[10-14] The resulting uncertainty about the comprehensive effect of age on the CKD-risk relationship hampers optimal clinical practice and public health initiatives for this large patient group.

Before general implementation of the recently revised CKD classification system,[7] acceptable clinical risk performance must be demonstrated in all age groups. The purpose of the current study is therefore to evaluate possible effect modification (interaction) by age of the association of eGFR and albuminuria with clinical risk, examining both relative and absolute risks. We analyzed data from more than 2 million participants in 46 different cohorts to characterize the mortal-

For editorial comment see p 2401.

Author Affiliations and a complete list of the Chronic Kidney Disease Prognosis Consortium appear at the end of this article.
Corresponding Author: Josef Coresh, MD, PhD, Chronic Kidney Disease Prognosis Consortium Data Coordinating Center, 615 N Wolfe St, Baltimore, MD 21205 (ckdpc@jhmi.edu).

ity and end-stage renal disease (ESRD) risks across the full age range (18-108 years) using a uniform analytic approach.

METHODS

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) consists of cohorts worldwide from general, high-risk (of vascular disease), and CKD populations with baseline information on eGFR and albuminuria, at least 1000 participants (not applied to CKD cohorts), and at least 50 events for any outcome of interest during follow-up (eAppendix 1; available at http://www.jama.com).[7,15-17] The CKD Epidemiology Collaboration (CKD-EPI) equation, with serum creatinine values standardized to isotope dilution mass spectrometry (IDMS) traceable methods, was used to estimate GFR.[18] For studies in which creatinine measurements were not standardized to IDMS, we reduced the creatinine levels by 5%, as previously reported.[19,20] Albuminuria was preferably measured as albumin-creatinine ratio (ACR), but studies with urine albumin excretion rate, urine protein-creatinine ratio (PCR), or dipstick protein were also included.

Information on demographic and cardiovascular risk factors was also obtained for all participants (eAppendix 2). Age was categorized as 18 to 54, 55 to 64, 65 to 74, and 75 or more years. Participants with missing values for either eGFR or albuminuria were excluded. Missing values for other adjustment variables were replaced by the cohort mean, as more advanced imputation methods were not feasible within this large consortium.

Our primary end points were all-cause mortality and ESRD; the latter was defined as initiation of dialysis, kidney transplantation, or death coded as due to kidney disease other than acute kidney injury. The results for cardiovascular mortality (death due to myocardial infarction, heart failure, sudden cardiac death, or stroke) are shown only in the supplemental online-only materials given the similarity to results for all-cause mortality. The study was based on deidentified information from studies previously approved by individual ethics boards, and the current meta-analysis was approved by the institutional review board at the Johns Hopkins Bloomberg School of Public Health.

In each study cohort, eGFR linear splines (knots at every 15 mL/min/1.73 m^2 from 30 to 105 mL/min/1.73 m^2 [90 mL/min/1.73 m^2 in CKD cohorts]) and their product terms with age category were incorporated in Cox proportional hazards models, providing hazard ratios (HRs) with eGFR of 80 mL/min/1.73 m^2 (50 mL/min/1.73 m^2 in CKD cohorts) selected as a stable reference for all age categories (eAppendix 2). Reference ranges are important for conducting statistical significance tests but do not alter the shape of the association across the full range of exposure. The CKD-PC usually uses the reference range of an eGFR of 90 to 104 mL/min/1.73 m^2 (95 mL/min/1.73 m^2 for continuous analysis) for general population and high-risk cohorts. However, given that few people (2.3%) in the oldest age category had eGFRs in this range and, thus, very few events (particularly ESRD) were observed in this eGFR range, we selected a lower eGFR of 80 mL/min/1.73 m^2 as the reference for the present study. Other covariates in the models were sex, race (black vs nonblack), history of cardiovascular disease, diabetes, systolic blood pressure, serum total cholesterol, body mass index, smoking, albuminuria (log-transformed ACR, PCR, or dipstick categories) and, for clinical trials, the randomized intervention.

Interactions (ie, effect modifications) were evaluated as the ratio of HRs in each age category compared with the age category of 55 to 64 years at each 1 mL/min/1.73 m^2 of eGFR from 15 to 120 mL/min/1.73 m^2 (pointwise interaction). Overall interaction for each age category compared with age 55 to 64 years across the full range of eGFR was assessed by averaging the coefficients for product terms between eGFR splines and age categories using inverse-variance weighting. Estimates from each cohort were pooled using random-effects models.

The same approach was applied to log-ACR risk associations, with knots at 10, 30, and 300 mg/g (30, 300, and 1000 mg/g in CKD cohorts) and the reference point of 10 mg/g (20 mg/g in CKD cohorts). Pointwise interaction of the ACR risk association was assessed at approximate 8% increments of ACR. The adjustment for eGFR was conducted using its spline terms. See eAppendix 2 for more details on analytical methods and individual cohorts.

We estimated the adjusted average absolute risk using the weighted average incidence rates in the reference age category (55-64 years) at the reference range of eGFR (75-89 mL/min/1.73 m^2) or ACR (<30 mg/g) combined with the meta-analyzed adjusted HRs for each level of eGFR and ACR. The weights were from the random-effects meta-analysis for HRs at adjacent points to the reference eGFR (80 mL/min/1.73 m^2) and ACR (10 mg/g) points in the spline models. For additive interaction, we tested whether the incidence rate difference was equal across age groups, and its direction was noted. The standard errors for additive interaction (incidence rate differences) were calculated using the delta method and the variance-covariance matrix of all the spline regression coefficients was obtained using multivariate meta-analysis and restricted maximum likelihood.[21] Because a single reference average incidence rate is combined with the adjusted HRs to obtain all of the adjusted average risks, the reference average incidence rate itself does not affect statistical tests of risk differences or interactions and was assumed to be constant in standard error calculations.

Categorical analyses comparing risks in 32 categories of eGFR (<15, 15-29, 30-44, 45-59, 60-74, 75-89, 90-104, and ≥105 mL/min/1.73 m^2) and albuminuria (ACR: <10, 10-29, 30-299, and ≥300 mg/g; PCR: <15, 15-49, 50-499, and ≥500 mg/g; or dipstick test results: negative, trace, 1+, ≥2+) were performed in general and high-risk cohorts. For mortality, we used eGFR of 75 to 89 mL/min/1.73 m^2 and the lowest albuminuria category as the reference. For ESRD, we used the no-CKD definition (eGFR ≥60 mL/min/1.73 m^2 and ACR <30 mg/g or equivalent proteinuria) as the reference because ESRD is rare at optimal kidney function.[1] Differences in absolute risks were calculated, and their standard errors were cal-

culated using the delta method using the variance-covariance matrix of the main effects and interactions obtained with multivariate meta-analysis.[21] Because there were few participants with an eGFR less than 15 mL/min/1.73 m^2 in the general population (<0.1%) and high-risk (0.2%) cohorts, we report results for this eGFR category only in the CKD cohorts. Heterogeneity was estimated by the χ^2 test for heterogeneity and the I^2 statistic. In all analyses, a 2-sided $P<.05$ was considered significant. All analyses were performed with Stata version 11.2 (StataCorp).

RESULTS

Forty-six cohorts (20 from North America, 12 from Europe, 10 from Asia, 1 from Australia, and 3 multinational) with 2 051 244 adults were included and followed up for a mean of 5.8 years during 1972-2011. Mean age was 49.4 years (range, 18-108 years, with 148 951 participants [7.3%] older than 75 years). The prevalences of diabetes, treated hypertension, and current smoking were 10.7%, 27.9%, and 21.5%, respectively. In general population and high-risk cohorts, older age was associated with lower mean eGFR and a higher prevalence of albuminuria (**TABLE 1**), history of cardiovascular disease, hypertension, diabetes, and other risk factors (eTable 1). Corresponding data for CKD cohorts are given in **TABLE 2** and eTable 1. There were a total of 112 325 deaths and 2766 ESRD events among the 33 general population cohorts and high-risk cohorts and an additional 9037 deaths and 5962 ESRD events in the 13 CKD cohorts.

FIGURE 1A and Figure 1B show adjusted relative hazards of all-cause mortality for eGFR and ACR. Mortality risk was higher at lower eGFRs and higher ACRs within each age category (18-54, 55-64, 65-74, and ≥75 years), but adjusted HRs were progressively lower at older ages. For example, HRs at an eGFR of 45 (vs 80) mL/min/1.73 m^2 were 3.50 (95% CI, 2.55-4.81) for age 18 to 54 years, 2.21 (95% CI, 2.02-2.41) for age 55 to 64 years, 1.59 (95% CI, 1.42-1.77) for age 65 to 74 years, and 1.35 (95% CI, 1.23-1.48) for age 75 years or older (see eFigure 1 for study-specific results).

Interaction was assessed both for each point in the graphs and overall compared with age 55 to 64 years as a reference. Pointwise age interaction was significant in a broad range of eGFRs (eg, a significant positive interaction and stronger effect for younger ages and negative interaction and weaker effect for older ages; Figure 1A). The differences among the 4 age categories were due to the difference in the slopes between eGFRs of 45 and 75 mL/min/1.73 m^2; the slopes at less than 45 mL/min/1.73 m^2 were largely parallel across the age categories. Nevertheless, the overall interaction was significant in all age categories compared with 55 to 64 years ($P<.004$ for all; eFigure 2, eFigure 3, and eFigure 4).

Despite this significant age interaction, mortality risk always started to increase in the eGFR range 60 to 75 mL/min/1.73 m^2, although in those aged 75 years or older it reached statistical significance only at an eGFR of 56 mL/min/1.73 m^2 or lower. Age interaction with ACR was less evident, and significant pointwise interaction was observed only at higher ACR ranges (Figure 1B). For example, HRs of all-cause mortality at an ACR of 300 (vs 10) mg/g were 2.53 (95% CI, 2.13-3.03) for age 18 to 54 years, 2.30 (95% CI, 1.84-2.88) for age 55 to 64 years, 2.10 (95% CI, 1.83-2.44) for age 65 to 74 years, and 1.73 (95% CI, 1.45-2.05) for age 75 years or older. Overall interaction reached significance only for age categories 65 to 74 years ($P=.02$) and 75 years or older ($P=.002$), showing lower relative hazards than age 55 to 64 years (eFigure 5, eFigure 6, and eFigure 7). The associations were consistent across subgroups determined by race, sex, and hypertension and diabetes status (eFigure 8, eFigure 9, eFigure 10, and eFigure 11).

Figure 1C and Figure 1D show all-cause mortality rates (absolute risk) for eGFR and ACR by age categories based on weighted averages across the cohorts, adjusted for covariates. A steeper slope at older age indicates a higher absolute risk difference associated with low eGFR compared with younger age categories. For example, at an eGFR of 45 (vs 80) mL/min/1.73 m^2, there were 9.0 (95% CI, 6.0-12.8) extra deaths per 1000 person-years in those aged 18 to 54 years, 12.2 (95% CI, 10.3-14.3) in those aged 55 to 64 years, 13.3 (95% CI, 9.0-18.6) in those aged 65 to 74 years, and 27.2 (95% CI, 13.5-45.5) in those aged 75 years or older. This pattern of higher absolute risk difference at older age for a worse kidney marker profile than the reference (positive interaction) and lower risk difference at younger age (negative interaction) was statistically significant for most eGFR values below 40 mL/min/1.73 m^2.

Figure 1D shows similar trends for high albuminuria with the additive interaction reaching statistical significance at all ACR values; the absolute risk differences of an ACR of 300 mg/g compared with 10 mg/g were 7.5 (95% CI, 4.3-11.9) for age 18 to 54 years, 12.2 (95% CI, 7.9-17.6) for age 55 to 64 years, 22.7 (95% CI, 15.3-31.6) for age 65 to 74 years, and 34.3 (95% CI, 19.5-52.4) for age 75 years or older. Studies with only older individuals demonstrated similar relative risk of mortality as other studies contributing to Figure 1 (eFigure 12). Relative and absolute risks of cardiovascular mortality were similar to those for all-cause mortality (eFigure 13).

FIGURE 2 shows relationships for ESRD. For ESRD, the adjusted HR started to increase at about an eGFR of 70 mL/min/1.73 m^2 and an ACR of 10 mg/g in all age categories (Figure 2A and Figure 2B). With the exception of slightly stronger association in the youngest age group within a limited range of eGFR (41-51 mL/min/1.73 m^2) and ACR (81-440 mg/g), no significant pointwise interactions were observed. Similar results were observed in the subset of cohorts in whom we conducted a competing risk analysis (eFigure 14). The oldest age category had the lowest HR associated with eGFR at 45 mL/min/1.73 m^2 but demonstrated steeper slope at an eGFR less than 45, catching up with other age categories by 15 mL/min/1.73 m^2 (Figure 2 and eFigure 15). Overall interactions for eGFR and ACR were not significant in the age categories of 18 to 54 years, 65 to 74 years, and 75 years or older compared with the reference age category of 55 to 64 years ($P=.11$ to .73; eFigure 16, eFigure 17, eFigure

18, eFigure 19, eFigure 20, and eFigure 21). The adjusted average ESRD incidence rate at a given level of eGFR or ACR was lower in the oldest age group (Figure 2C and Figure 2D). However, the differences in absolute risk were not significant except for a limited GFR range in which the adjusted average ESRD incidence rate was higher in the youngest age group.

Similar findings were observed when we tested age interactions with combined categories of eGFR and albuminuria (FIGURE 3 and eTable 2). Specifically, relative associations with all-cause mortality were often strongest (brown shading) in the youngest; conversely, absolute risks were highest at older age with low eGFR and high albuminuria, although differences compared with age 55 to 64 years were statistically significant only for a subset of the categories. For ESRD, the associations with both eGFR and ACR were very strong

Table 1. Baseline Characteristics of Participating General Population and High-Risk Cohorts by Age Group

			Age Group, y											
			18-54			55-64			65-74			≥75		
Source	No. of Participants	Follow-up, y	% of Total	Mean eGFR	Albuminuria, %[a]	% of Total	Mean eGFR	Albuminuria, %[a]	% of Total	Mean eGFR	Albuminuria, %[a]	% of Total	Mean eGFR	Albuminuria, %[a]
General population cohorts														
Aichi[22]	4731	7.4	81	99	2	19	90	3	<0.01	94	0	NA	NA	NA
AKDN[23]	920 686	2.7	66	93	4	16	77	4	10	68	6	8	58	10
ARIC[24,b]	11 441	10.6	6	93	6	55	87	7	40	78	11	<0.01	72	33
AusDiab[25,b]	11 179	9.9	61	94	4	18	81	6	14	72	11	7	63	24
Beaver Dam CKD[26]	4857	11.6	31	91	3	27	82	3	26	74	5	16	63	7
Beijing[27,b]	1559	3.9	34	93	5	30	82	5	32	76	7	4	68	7
CHS[28,b]	2988	8.4	NA	NA	NA	NA	NA	NA	25	80	18	75	72	21
CIRCS[29]	11 871	17.0	51	96	3	36	84	3	14	78	4	NA	NA	NA
COBRA[30,b]	2872	4.1	66	110	6	19	96	14	11	87	14	4	78	23
ESTHER[31]	9641	5.0	17	92	9	44	86	11	38	78	14	1	70	20
Framingham[32,b]	2956	10.5	37	99	7	33	88	10	25	77	19	5	67	30
Gubbio[33,b]	1681	10.7	50	88	3	50	81	5	NA	NA	NA	NA	NA	NA
HUNT[3,b]	9659	12.0	30	103	5	20	87	9	30	78	14	21	69	23
IPHS[34]	95 451	14.0	34	96	2	31	85	2	30	78	3	5	70	4
MESA[35,b]	6733	6.2	28	92	5	28	84	8	30	77	11	14	69	18
MRC[36]	12 371	6.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	100	57	7
NHANES III[37,b]	15 563	8.5	65	113	7	13	88	15	13	77	20	10	66	27
Ohasama[38]	1956	10.4	17	94	12	42	85	6	31	79	5	10	69	19
Okinawa 83[39]	9599	16.9	58	84	15	19	69	24	15	62	29	8	55	36
Okinawa 93[40]	93 216	6.9	46	87	3	25	74	4	19	67	5	10	58	6
PREVEND[41,b]	8385	9.7	66	95	7	18	81	15	16	73	25	0.01	61	35
Rancho Bernardo[42,b]	1474	10.5	11	88	4	25	81	9	26	73	15	39	64	21
REGARDS[43,b]	27 306	5.1	12	100	10	38	91	12	32	80	16	17	70	22
Severance[44]	76 201	10.0	74	93	5	20	82	6	5	75	7	1	66	13
Taiwan[45]	515 573	8.1	79	98	1	13	79	4	6	70	6	1	61	7
ULSAM[46,b]	1103	11.6	NA	NA	NA	NA	NA	NA	100	76	16	NA	NA	NA
Total[c]	1 861 052	5.9 (0.003-20.8)	65	95 (16)	3	18	79 (15)	4	11	71 (15)	7	6	60 (16)	11
High-risk cohorts														
ADVANCE[47,b]	10 595	4.8	0.01	83	24	40	85	32	50	75	29	9	66	33
AKDN (ACR)[23,b,d]	102 639	3.0	44	90	20	24	76	23	19	65	28	12	55	39
CARE[48]	4098	4.8	32	86	10	37	75	14	30	67	17	1	59	30
KEEP[49]	77 902	4.2	50	98	10	23	81	12	17	72	15	10	61	21
KP Hawaii[50,e]	39 884	2.4	38	94	34	27	78	29	20	68	32	16	58	40
MRFIT[51]	12 854	24.9	91	88	4	9	80	3	NA	NA	NA	NA	NA	NA
Pima[52,b]	5066	13.8	91	124	17	6	91	46	3	82	53	1	72	53
ZODIAC[53,b]	1095	7.9	13	92	23	21	78	30	34	69	42	31	59	50
Total[c]	254 133	4.4 (0.003-32.0)	46	94 (20)	17	24	79 (17)	21	19	69 (17)	25	11	58 (17)	34

Abbreviation: NA, data not applicable.
[a] Percentage of participants with albumin-creatinine ratio ≥30 mg/g, protein-creatinine ratio ≥50 mg/g, or dipstick protein ≥1+.
[b] Studies measuring albumin-creatinine ratio.
[c] Total number of participants. Overall mean for percentages. Overall mean with range or SD for continuous variables.
[d] All participants with albumin-creatinine ratio measurements in this study were counted in the larger dipstick data pool and thus are not accounted for in the overall total number of participants.
[e] Studies measuring protein-creatinine ratio.

in all age groups, with effect modification by age being more subtle, with 3 of 15 categories showing weaker relative hazards at older ages (65-74 and ≥75 years) and fewer (3 at age 65-74 years and none at age ≥75 years) showing lower ESRD risk difference compared with the same category at age 55 to 64 years (eFigure 22).

FIGURE 4 shows a separate analysis of CKD cohorts using a lower reference point for eGFR (50 mL/min/1.73 m^2). The slopes for relative risk of mortality were largely parallel across age categories, indicating no age interaction. Somewhat steeper slope was observed at older age categories for ESRD, although overall interactions were of borderline significance (P=.04 for age 18-54 years, P=.07 for age 65-74 years, and P=.08 for age ≥75 years vs 55-64 years). Absolute mortality risk was higher at older age, but the risk difference (additive interaction) was largely nonsignificant (Figure 4C). For ESRD, at moderately reduced eGFR the youngest age group had the highest adjusted average incidence rate but had similar HRs as the other age categories because of a higher risk at the reference eGFR. The risk increased steeply among older individuals, leading to comparable absolute risks around an eGFR of 15 mL/min/1.73 m^2. Analysis of increasing levels of albuminuria in patients with CKD showed similar patterns with the caveat that only a few CKD cohorts had ACR measured (eFigure 23).

COMMENT

In this large collaborative meta-analysis, low eGFR and high albuminuria were associated with mortality and ESRD regardless of age. We found that mortality risk associations were weaker on the relative scale but stronger on the absolute scale at older ages in general population and high-risk cohorts. In cohorts specifically selected for CKD, age did not modify the mortality associations. For ESRD risk, age did not significantly influence relative and absolute risk gradients. Thus, eGFR and albuminuria were strongly associated with both mortality and ESRD in a wide range of studies across the full age range. Importantly, the results were largely consistent across diverse cohorts in terms of demographic and clinical characteristics.

In principal, CKD diagnosis could be based on (1) "normal" values based on the distribution in apparently healthy individuals or (2) kidney marker levels associated with increased risk of future adverse outcomes.[67] Supporters of the former approach have cited a dramatic rise in the prevalence of nephrosclerosis with age in kidney biopsies, even among healthy kidney donors, and have proposed the concept of natural inevitable senescence of the kidneys, suggesting age-specific cutoffs for defining normal kidney function.[14] Several studies suggesting that the relative mortality risk associated with low eGFR is reduced at older ages have also been used as arguments for age-specific CKD diagnosis and staging.[10,12,13,45] In contrast, our meta-analysis documents that risk of mortality and ESRD is increased

Table 2. Baseline Characteristics of Participating Chronic Kidney Disease Cohorts by Age Group

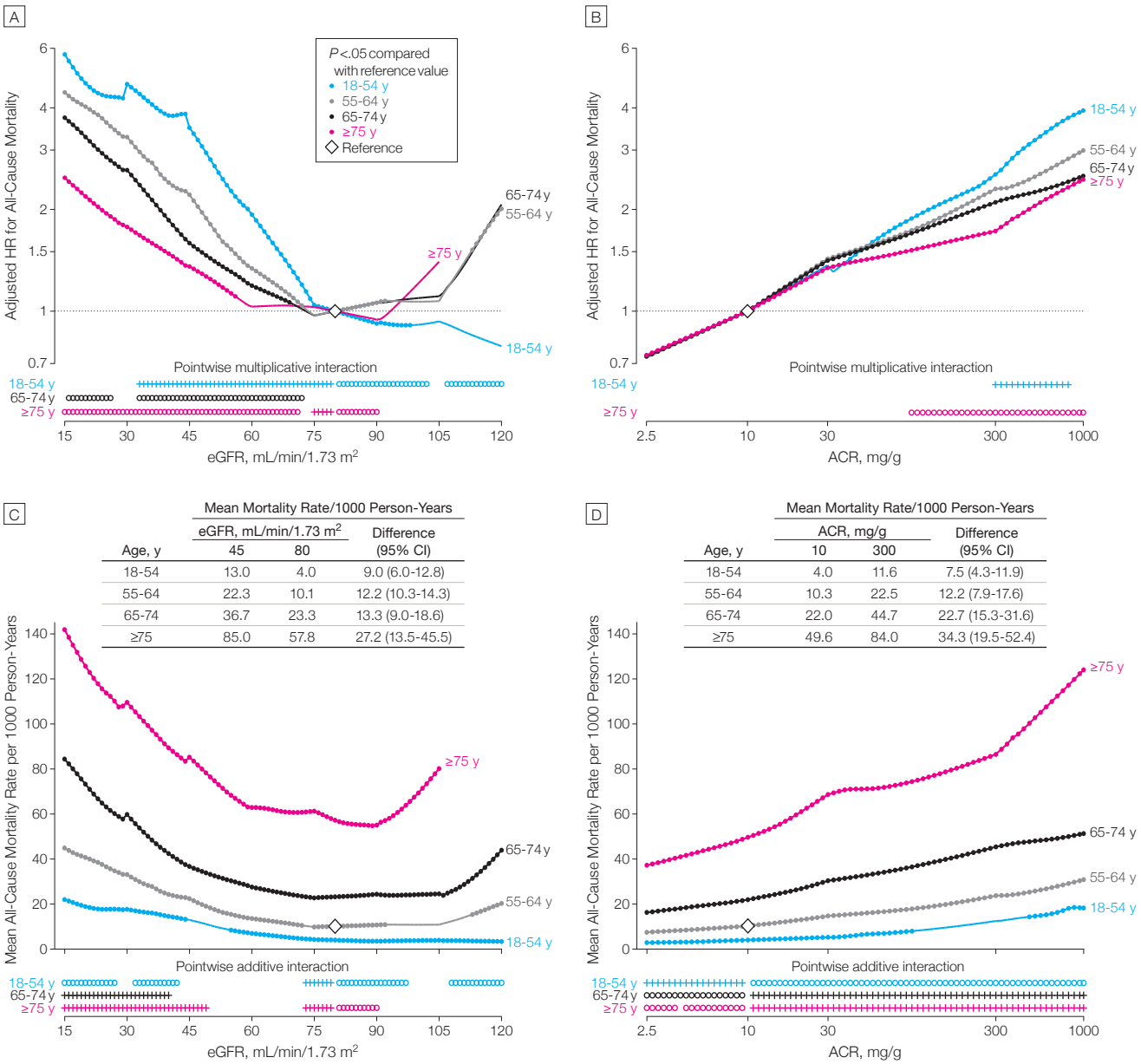
			Age Group, y											
			18-54			55-64			65-74			≥75		
Source	No. of Participants	Follow-up, y	% of Total	Mean eGFR	Albuminuria, %[a]	% of Total	Mean eGFR	Albuminuria, %[a]	% of Total	Mean eGFR	Albuminuria, %[a]	% of Total	Mean eGFR	Albuminuria, %[a]
AASK[54,b]	1094	8.8	48	45	72	33	47	54	20	46	49	NA	NA	NA
BC CKD[55]	17 426	3.3	15	47	87	17	41	79	28	37	72	40	31	71
CRIB[56,c]	308	6.1	30	24	95	21	23	83	29	22	84	21	20	81
Geisinger[57]														
Measuring albumin-creatinine ratio[c]	3361	3.5	7	49	62	20	51	44	36	51	41	38	50	42
Dipstick protein measurement	4509	3.9	7	45	45	14	49	28	28	50	23	50	49	23
GLOMMS-1[58]														
Measuring albumin-creatinine ratio[c]	537	4.2	5	38	71	14	36	59	34	34	47	47	30	48
Measuring protein-creatinine ratio[b]	470	4.2	16	32	92	13	31	100	27	30	91	44	27	97
KPNW[59]	1627	4.6	6	47	54	14	49	38	36	48	31	44	44	27
MASTERPLAN[60,c]	636	4.1	29	37	94	28	37	84	34	36	79	9	35	84
MDRD[61,b]	1730	14.1	57	43	86	28	38	78	15	38	74	NA	NA	NA
MMKD[62,b]	202	4.0	67	52	95	31	39	95	1	16	100	NA	NA	NA
NephroTest[63,c]	928	2.6	34	49	71	25	42	63	25	40	58	16	33	57
RENAAL[64,c]	1513	2.8	22	44	100	44	41	100	34	39	100	NA	NA	NA
STENO[65,c]	886	8.8	85	86	52	11	77	33	4	65	41	1	73	0
Sunnybrook[66,c]	3385	2.3	13	43	88	16	41	84	26	38	83	44	33	84
Total[d]	38 612	4.2 (0.003-18.9)	19	49 (27)	79	19	43 (18)	70	28	41 (16)	62	35	37 (14)	59

Abbreviation: NA, data not applicable.
[a] Percentage of participants with albumin-creatinine ratio ≥30 mg/g, protein-creatinine ratio ≥50 mg/g, or dipstick protein ≥1+.
[b] Studies measuring protein-creatinine ratio.
[c] Studies measuring albumin-creatinine ratio.
[d] Total number of participants. Overall mean for percentages. Overall mean with range or SD for continuous variables.

at approximately 60 mL/min/1.73 m^2, the threshold used for defining CKD during the last 10 years, across all age groups. In fact, at the oldest age group, although relative risks of mortality are lowest, attributable risks are highest. Therefore, while economic and other considerations should be taken into account, in terms of risks of mortality and ESRD, our data support the current thresholds for defining and staging CKD.

We provided both relative and absolute risk estimates because they complement each other. Relative risks are more generalizable across different settings[68] (high and low baseline risk and varying duration of follow-up), while absolute risks are concrete, easy-to-understand estimates that guide cost-benefit analyses and estimates of the potential for prevention. An attenuation of the relative mor-

Figure 1. Adjusted Hazard Ratios (HRs) for All-Cause Mortality and Mean Mortality Rates According to eGFR and ACR Within Each Age Category

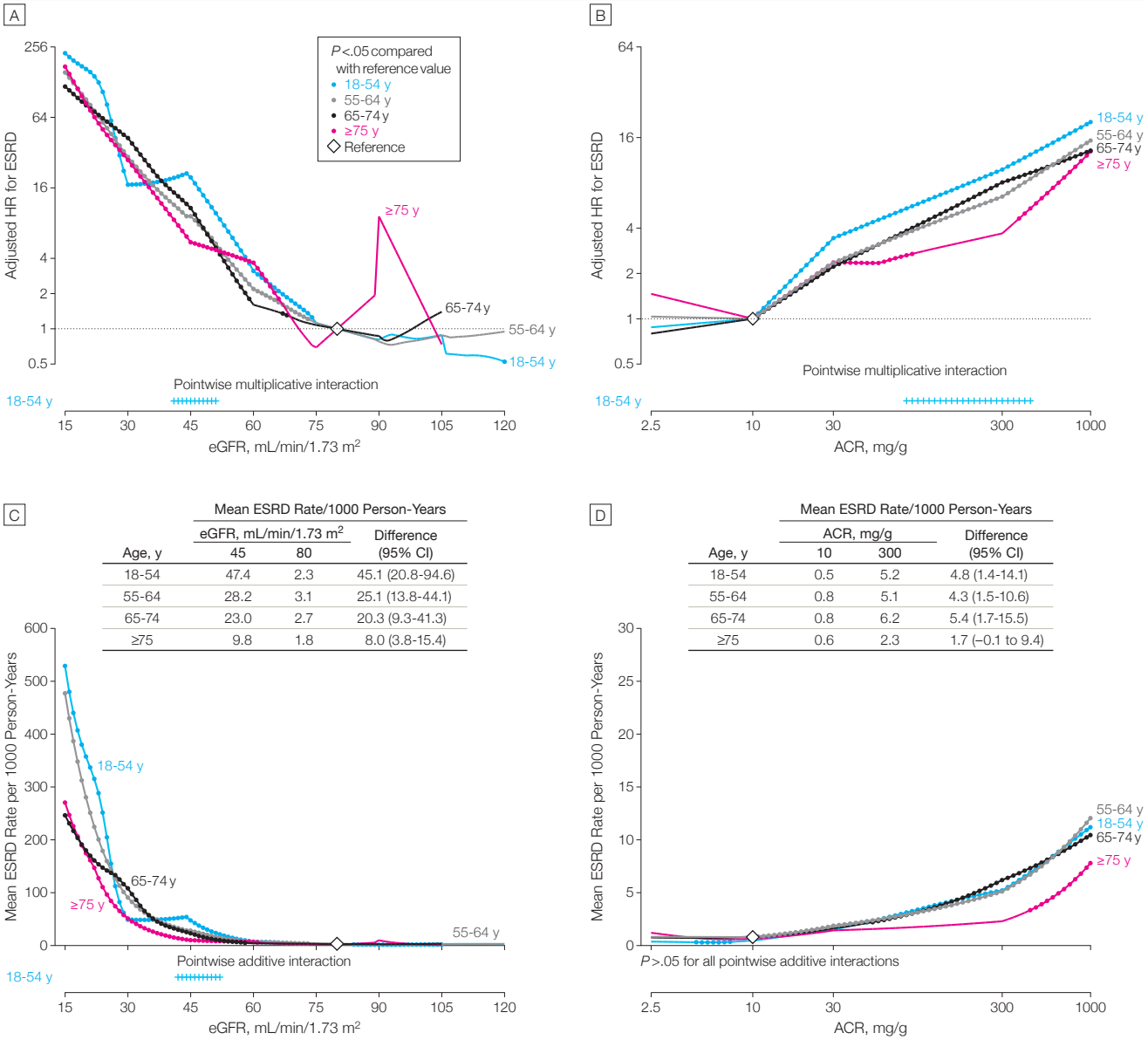


Filled circles denote statistical significance ($P<.05$) compared with the reference (diamond) estimated glomerular filtration rate (eGFR) of 80 mL/min/1.73 m^2 or albumin-creatinine ratio (ACR) of 10 mg/g within each age category in A and B and compared with the age category of 55 to 64 years in C and D. Plus signs and open circles at the bottom of each graph represent significantly positive (greater effect size) and negative (smaller effect size) pointwise interactions ($P<.05$), respectively, compared with age 55 to 64 years. Gaps indicate no significant pointwise interaction. Models are meta-analysis of general population and high-risk cohorts adjusted for sex, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria (A and C) or eGFR (B and D).

tality risk associated with low eGFR was found with increasing age, as shown for traditional cardiovascular risk factors.[69] This lower relative risk at older age may result from a higher absolute risk in the reference population due to higher comorbidities, even at optimal kidney function. However, absolute risk differences (excess deaths per 1000 person-years) were higher among older people. Similar relative risk attenuations but absolute risk increases have been found with older age for cardiovascular risk factors such as hypertension, hypercholesterolemia, and obesity,[70] yet clinical guidelines do not advocate age-specific "normality"-based cutoffs for these risk factors but rather use "risk-based" cutoffs.

The similarity of our results for eGFR support a similar approach for defining CKD. For example, even at age 75 years or older, persons with eGFR of 45 to 59 mL/min/1.73 m^2 and optimally low albuminuria had significantly increased mortality risk, although they had lower relative hazards and higher absolute risks than at

Figure 2. Adjusted Hazard Ratios (HRs) and Mean Incidence Rates for ESRD According to eGFR and ACR Within Each Age Category



Filled circles denote statistical significance ($P < .05$) compared with the reference (diamond) estimated glomerular filtration rate (eGFR) of 80 mL/min/1.73 m^2 or albumin-creatinine ratio (ACR) of 10 mg/g within each age category in A and B and compared with the age category of 55 to 64 years in C and D. Plus signs and open circles at the bottom of each graph represent significantly positive (greater effect size) and negative (smaller effect size) pointwise interactions ($P < .05$), respectively, compared with age 55 to 64 years. Gaps indicate no significant pointwise interaction. Models are meta-analysis of general population and high-risk cohorts adjusted for sex, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria (A and C) or eGFR (B and D).

younger ages. Furthermore, our CKD cohorts showed no attenuation of relative risks with age. On the other end of the eGFR spectrum, our study confirms that very high eGFR values are associated with increased relative and absolute mortality risk in patients older than 55 years. This is likely caused by the influence of patients with reduced muscle mass due to malnutrition and other effects associated with cancer or other significant comorbidities. Risk implications of high eGFR values should therefore be interpreted with caution.

Most[10,11,16,71-73] but not all[36,74] studies found a significant association of mortality risk with higher levels of albuminuria among older individuals. The higher risk with albuminuria has been found across all age groups and eGFR levels,[10] and in elderly participants from diabetes, nondiabetes, and community-based cohorts.[10,11,71,72] It has been suggested that the optimal cutoff for predicting death is lower than the cutoff for defining CKD.[73] The current meta-analysis did not assess the most optimal cutoff but established that the risk association is linear on the log-log scale with no thresholds. Variation in relative hazards with age was modest and limited to very high albuminuria, while excess mortality associated with albuminuria was consistently higher at older ages.

Lower ESRD risk at a given level of eGFR has been reported at old age,[13,15,75] and treatment recommendations have been cautious in patients aged 70 years or older with moderately reduced eGFR.[1,76] We found a trend toward lower ESRD risk at age 75 years or older, which may be partially due to higher mortality risk at older age (competing risk). Also, several clinical or social factors other than kidney function may affect the decision to initiate kidney replacement therapy, particularly in older individuals. A recent analysis of the Alberta Kidney Disease Network focused on showing that untreated kidney failure and its ratio to ESRD increased dramatically with age.[77] Importantly, the adjusted HRs for ESRD associated with low eGFR were similar across age groups in our analysis. We also did not find age differences in the ESRD risk gradient associated with high albuminuria. The current analysis expands on previous work by looking at both eGFR and albuminuria and contrasting mortality and ESRD associations. Importantly, using individual-level reanalysis of data from 40 countries, we were able to obtain definitive results with a global context.

Our findings have several important implications. First, our study shows that the kidney measures used for defining and staging CKD are strong predictors of clinical risk across the full age range, including age 75 years or older in many cohorts.

Figure 3. Adjusted Hazard Ratios and Mean Incidence Rate Differences for All-Cause Mortality by Categories of Estimated Glomerular Filtration Rate (eGFR) and Albuminuria Across Age Groups

A Adjusted hazard ratios

	Albumin-Creatinine Ratio															
	Age 18-54 y				Age 55-64 y				Age 65-74 y				Age ≥75 y			
	<10	10-29	30-299	≥300	<10	10-29	30-299	≥300	<10	10-29	30-299	≥300	<10	10-29	30-299	≥300
eGFR, mL/min/1.73 m^2																
≥105	*0.89*[a]	*1.37*	2.83	5.62	1.58	2.17	3.64	5.68	*1.61*	2.28	2.83	12.21	*1.63*	*0.76*	24.27	
90-104	*1.04*[a]	1.78	2.23	3.68	1.14	1.42	2.10	4.48	*1.01*[a]	1.62	1.83	2.98	*0.97*	1.88	2.18	6.77
75-89	1 [Ref]	1.78	2.25[b]	3.77[b]	1 [Ref]	1.47	1.80	3.42	1 [Ref]	1.38	1.92	2.85	1 [Ref]	1.49	1.91[b]	2.73
60-74	1.37[b]	2.25[b]	3.60[b]	7.30[b]	1.08	1.55	2.60	4.24	*1.04*[a]	1.50	1.89[a]	2.95[a]	*1.04*	1.48	1.83[a]	2.66[a]
45-59	2.79[b]	4.33[b]	10.05[b]	9.48[b]	1.58	2.55	3.38	5.16	1.19[a]	1.86[a]	2.49[a]	3.49[a]	1.20[a]	1.75[a]	1.91[a]	2.76[a]
30-44	8.19[b]	12.59[b]	12.62[b]	15.48[b]	3.39	4.03	6.96	6.49	2.00[a]	3.18	4.14[a]	4.56[a]	1.71[a]	2.41[a]	2.73[a]	3.41[a]
15-29	11.98	16.13	17.35[b]	19.40[b]	7.01	6.78	8.27	9.89	3.86[a]	4.44	5.83	6.19[a]	2.90[a]	3.69[a]	3.67[a]	5.29[a]

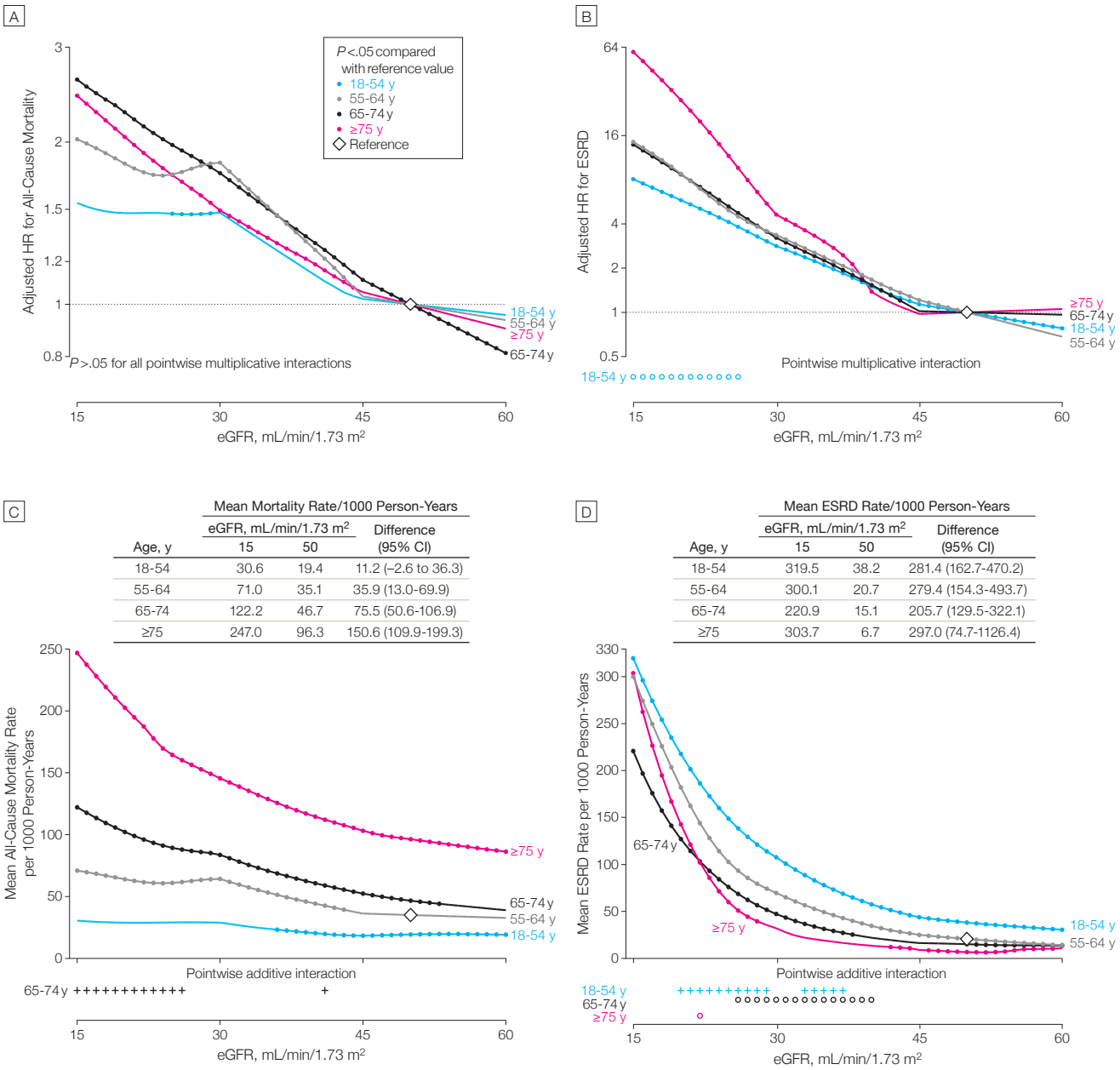
B Incidence rate difference per 1000 person-years

	Albumin-Creatinine Ratio															
	Age 18-54 y				Age 55-64 y				Age 65-74 y				Age ≥75 y			
	<10	10-29	30-299	≥300	<10	10-29	30-299	≥300	<10	10-29	30-299	≥300	<10	10-29	30-299	≥300
eGFR, mL/min/1.73 m^2																
≥105	*−0.35*[a]	1.18	5.77[a]	14.56	5.34	10.76	24.31	43.07	*13.92*	29.12	41.51	254.86	*33.80*	*−13.18*	1254.90	
90-104	*0.12*[a]	2.46[a]	3.87[a]	8.44[a]	1.26	3.83	10.14	31.98	*0.33*	14.18[b]	18.87	45.03	*−1.56*	47.37	63.45	310.90
75-89	0 [Ref]	2.45[a]	3.92[a]	8.72[a]	0 [Ref]	4.31	7.32	22.24	0 [Ref]	8.62	20.85[b]	42.00[b]	0 [Ref]	26.55[b]	49.08[b]	93.29[b]
60-74	1.17	3.93	8.18[a]	19.85[a]	0.73	5.08	14.68	29.77	*0.97*	11.26[b]	20.30	44.38[b]	*2.32*	25.74[b]	44.98[b]	93.29[b]
45-59	5.62	10.50	28.49	26.72[a]	5.35	14.25	21.88	38.24	4.36	19.61	33.91[b]	56.58[b]	10.99	40.57[b]	48.89[b]	94.98[b]
30-44	22.63	36.49	36.59	45.60	21.97	27.92	54.85	50.49	22.86	49.57[b]	71.36	80.91[b]	38.03[b]	75.88[b]	93.18	129.99[b]
15-29	34.58[a]	47.64	51.48	57.95[a]	55.30	53.16	66.85	81.76	65.09	78.22	109.80[b]	118.00	102.23	145.14[b]	143.83[b]	231.47[b]

Each number represents a pooled estimate from meta-analysis in 33 general population and high-risk cohorts. All results are adjusted for covariates. Dipstick results corresponding to albumin-creatinine ratios (ACRs) are as follows: for ACR <10 mg/g, dipstick negative (–); for ACR 10-29 mg/g, dipstick trace (±); for ACR 30-299 mg/g, dipstick positive (1+); and for ACR ≥300, dipstick positive (≥2+). Data are statistically significant at $P<.05$ compared with the reference unless italicized; "a" indicates a significant negative interaction and "b" indicates a significant positive interaction at $P<.05$ compared with the corresponding cell at age 55 to 64 years. Color shading indicates the strength of association (approximately one-quarter of all cells are shaded in each color; lightest color [beige] indicates low; blue, mild; tan, moderate; and darkest color [brown], high) measured as either hazard ratios (A) or incidence rate difference (B). Confidence intervals are provided in eTable 2.

This contradicts concerns raised by some that current CKD guidelines should be used with caution in older individuals and that low eGFR reflects only natural aging.[12,74,75,78,79] Relating variation in kidney function at older age to subsequent outcomes is the best way to distinguish kidney health from disease without relying on theoretical arguments of what is natural. Second, our data support the recommendations from several investigators that CKD measures should be added to mortality risk equations.[80,81] This is, however, still debated,[82,83] and our meta-analysis did not assess the incremental prognostic value of adding CKD markers. Third, the strong increase in mortality rate along with kidney measures at older ages suggests that

Figure 4. Adjusted Hazard Ratios (HRs) and Mean Incidence Rates for All-Cause Mortality and ESRD in CKD Cohorts According to eGFR Within Each Age Category



Filled circles denote statistical significance ($P<.05$) compared with the reference (diamond) estimated glomerular filtration rate (eGFR) of 50 mL/min/1.73 m^2 within each age category in A and B and compared with the age category of 55 to 64 years in C and D. Plus signs and open circles at the bottom of each graph represent significantly positive (greater effect size) and negative (smaller effect size) pointwise interactions ($P<.05$), respectively, compared with age 55 to 64 years. Gaps indicate no significant pointwise interaction. Models are meta-analysis of chronic kidney disease (CKD) cohorts adjusted for sex, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria.

older adults should not be left out from management strategies of CKD. Previous data show that low eGFR in the very old is associated with classical CKD complications like anemia, acidosis, hyperparathyroidism, and hyperphosphatemia.[84] There is also an increasing risk of untreated kidney failure with age,[77] which may be more common in general population cohorts than cohorts selected for CKD, further supporting this view. Overall, the current risk-based system for defining and staging CKD is supported by robust evidence across the full age range. Relying on 1 common CKD classification system for all age groups facilitates implementation in general practice, but clearly intensity and type of treatment could differ by age owing to remaining lifetime and comorbidities. Nevertheless, further studies are needed to elucidate whether interventions to prevent CKD progression or CKD-related outcomes are similarly effective and cost-effective across age categories. Although we evaluated critical clinical outcomes, studies taking into account quality of life would be warranted, particularly for older age groups.

Some limitations of our study need to be discussed. Serum creatinine measurements were not standardized in all studies. However, we observed similar results when we limited our analysis to studies with serum creatinine measurements standardized to IDMS (data not shown). There is also concern about validity of the CKD-EPI equation in older individuals. However, a recent article reported that the CKD-EPI equation may be as accurate in older individuals as in younger individuals.[85]

Another limitation is that there is no internationally accepted gold standard method for measuring urine albumin, and sampling and storage of urine were not standardized. Many cohorts also used dipstick, which is a semiquantitative method, for assessing albuminuria, limiting numbers of participants in the analysis for ACR as a continuous variable. Therefore, misclassification of albuminuria, particularly for categorical analysis, might exist.

In addition, heterogeneity across cohorts in absolute and relative risks is present and needs to be considered, but our random-effects meta-analysis conservatively incorporates heterogeneity into its confidence interval calculations. Likewise, differences in study quality could have influenced our results. Furthermore, results were consistent across cohort types and after exclusion of the largest cohort.

A further limitation is that our results need to be carefully interpreted given that they were based on models adjusting for traditional risk factors. However, the results were largely similar when we adjusted only for sex and race (data not shown). Absolute risk at the reference point calculated as a weighted average of the cohorts may not directly apply to any single setting. The shape of the associations and tests for interactions in the present meta-analysis are independent of the exact risk at the reference point. However, the current meta-analysis is not intended to develop an individual risk prediction tool. The incidence rate differences reported are conservative because they adjust for covariates, and unadjusted differences may be larger. We did not confirm the validity of proportional hazards assumption for every study, although some of the collaborating cohorts individually confirmed this assumption for clinical risk with eGFR and/or albuminuria as predictors.[16] Thus, the pooled HRs in this study estimate the average HR over follow-up time.

The study is strengthened by showing consistent results across ACR, PCR, and dipstick cohorts. We evaluated CKD-age interaction on both relative and absolute scales. Moreover, inclusion of more than 2 million participants worldwide increases precision and generalizability of estimates to a level that previously has not been possible, particularly for the very old and for ESRD. Individual-level data, common definitions of covariates, and uniform analysis with adjustment for major risk factors further strengthen our study. We also used the CKD-EPI formula for estimating GFR, which improves the accuracy of kidney function estimates and overall risk prediction[19,86] and has not been examined for age interaction in most cohorts.

In summary, our analysis of more than 2 million individuals from 46 cohorts across the world shows that CKD markers were associated with risk across the full age spectrum. There was no effect modification for ESRD risk, while relative mortality risk decreased with age. However, absolute mortality risk difference tended to increase with age. Although some variation in management of CKD should be considered by age based on cost and benefits, with respect to risk of mortality and ESRD, our data support a common definition and staging of CKD based on eGFR and albuminuria for all age groups.

Published Online: October 30, 2012. doi:10.1001/jama.2012.16817

Author Affiliations: Division of Nephrology, Department of Medicine, St Olav University Hospital, and Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway (Dr Hallan); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Drs Matsushita, Mahmoodi, and Coresh and Ms Sang); Department of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands (Drs Mahmoodi and Gansevoort); Aberdeen Applied Renal Research Collaboration, Division of Applied Health Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland (Dr Black); Center for Epidemiology and Clinical Research, Minneapolis VAMC and University of Minnesota, Minneapolis (Dr Ishani); Diabetes Centre, Isala Clinics, and Langerhans Medical Research Foundation, Zwolle, the Netherlands (Dr Kleefstra); Department of Internal Medicine, University Medical Center Groningen, Groningen, the Netherlands (Dr Kleefstra); Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada (Dr Naimark); Public Health Sciences and Medical Statistics, University of Southampton, University Hospital Southampton, Southampton, England (Dr Roderick); Department of Medicine, University of Alberta, Edmonton, Canada (Dr Tonelli); Department of Nephrology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands (Dr Wetzels); Departments of Medicine and Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison (Dr Astor); Department of Medicine, St Paul's Hospital, University of British Columbia, Vancouver, Canada (Dr Levin); Institute of Population Science, National Health Research Institutes, Zhunan, Taiwan (Dr Wen); and China Medical University Hospital, Taichung, Taiwan (Dr Wen).

Author Contributions: Dr Coresh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Matsushita, Astor, Gansevoort, Levin, Wen, Coresh.
Acquisition of data: Matsushita, Coresh (for CKD-PC, with CKD-PC investigators/collaborators listed below).
Analysis and interpretation of data: Hallan, Matsushita, Sang, Mahmoodi, Black, Ishani, Kleefstra, Naimark, Roderick, Tonelli, Wetzels, Astor, Gansevoort, Levin, Wen, Coresh.
Drafting of the manuscript: Hallan, Matsushita, Gansevoort, Coresh.
Critical revision of the manuscript for important intellectual content: Hallan, Matsushita, Sang, Mahmoodi, Black, Ishani, Kleefstra, Naimark, Roderick, Tonelli, Wetzels, Astor, Gansevoort, Levin, Wen, Coresh.

Statistical analysis: Matsushita, Sang, Coresh (with Data Coordinating Center members listed below).
Obtained funding: Matsushita, Coresh (for CKD-PC, with cohort and collaborator support listed in eAppendix 3).
Administrative, technical, or material support: Matsushita, Sang, Coresh.
Study supervision: Matsushita, Gansevoort, Coresh.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Matsushita reports receiving grant support to his institution from the National Kidney Foundation (NKF) and Amgen and to him from the National Institutes of Health; Dr Mahmoodi, grant support from the Netherlands Organization for Scientific Research and the Dutch Kidney Foundation; Dr Black, grant support to her institution from CKD-PC/KDIGO; Dr Ishani, travel support from the NKF; Dr Naimark, a stipend for data analysis from the NKF/CKD-PC and payment for expert testimony from the College of Physicians and Surgeons of Newfoundland and Labrador; Dr Roderick, grant support to his institution from Kidney Research UK, Dr Tonelli, grant support to his institution from Johns Hopkins University; Dr Wetzels, grant support to his institution from Amgen, Pfizer, and Sanofi-Genzyme; Dr Gansevoort, grants and consultancy/lecture fees to his institution from Otsuka, Bayer, Amgen, Baxter, Abbott, and Roche and payment to him for educational materials or travel expenses from Roche, Amgen, and Bayer; Dr Wen, grant support to his institution from the Taiwan Department of Public Health Clinical Trial and Research Center of Exellence; and Dr Coresh, grant support to his institution from the NKF and Amgen and payment to him for consultancy fees from Amgen and Merck. No other disclosures were reported.
CKD-PC Investigators/Collaborators (study abbreviations are listed in eAppendix 1): *AASK* (United States): Jackson T. Wright Jr, Lawrence J. Appel, Tom Greene, Brad C. Astor; *ADVANCE* (Australia): John Chalmers, Stephen MacMahon, Mark Woodward, Hisatomi Arima; *Aichi Workers Cohort* (Japan): Hiroshi Yatsuya, Kentaro Yamashita, Hideaki Toyoshima, Koji Tamakoshi; *AKDN* (Canada): Marcello Tonelli, Brenda R. Hemmelgarn, Aminu Bello, Matthew T. James; *ARIC* (United States): Josef Coresh, Brad C. Astor, Kunihiro Matsushita, Yingying Sang; *AusDiab Study* (Australia): Robert C. Atkins, Kevan R. Polkinghorne, Steven Chadban; *Beaver Dam CKD Study* (United States): Anoop Shankar, Ronald Klein, Barbara E. K. Klein, Kristine E. Lee; *Beijing Cohort Study* (China): Haiyan Wang, Fang Wang, Luxia Zhang, Li Zuo; *British Columbia CKD Study* (Canada): Adeera Levin, Ognjenka Djurdjev; *CARE* (United States/Canada): Marcello Tonelli, Frank M. Sacks, Gary C. Curhan; *CHS* (United States): Michael Shlipak, Carmen Peralta, Ronit Katz, Linda F. Fried; *CIRCS* (Japan): Hiroyasu Iso, Akihiko Kitamura, Tetsuya Ohira, Kazumasa Yamagishi; *COBRA* (Pakistan/United Kingdom): Tazeen H. Jafar, Muhammad Islam, Juanita Hatcher, Neil Poulter, Nish Chaturvedi; *CRIB* (United Kingdom): Martin J. Landray, Jonathan Emberson, Jonathan N. Townend, David C. Wheeler; *ESTHER* (Germany): Dietrich Rothenbacher, Hermann Brenner, Heiko Müller, Ben Schöttker; *Framingham Heart Study* (United States): Caroline S. Fox, Shih-Jen Hwang, James B. Meigs; *Geisinger CKD Study* (United States): Robert M. Perkins; *GLOMMS-1 Study* (United Kingdom): Nick Fluck, Laura E. Clark, Gordon J. Prescott, Angharad Marks, Corri Black; *Gubbio Study* (Italy): Massimo Cirillo; *HUNT* (Norway): Stein Hallan, Knut Aasarød, Cecilia M. Øien, Maria Radtke; *IPHS* (Japan): Fujiko Irie, Hiroyasu Iso, Toshimi Sairenchi, Kazumasa Yamagishi; *Kaiser Permanente Northwest* (United States): David H. Smith, Jessica W. Weiss, Eric S. Johnson, Micah L. Thorp; *KEEP* (United States): Allan J. Collins, Joseph A. Vassalotti, Suying Li, Shu-Cheng Chen; *Kaiser Permanente Hawaii Cohort* (United States): Brian J. Lee; *MASTERPLAN* (Netherlands): Jack F. Wetzels, Peter J. Blankestijn, Arjan D. van Zuilen; *MDRD* (United States): Mark Sarnak, Andrew S. Levey, Lesley A. Inker, Vandana Menon; *MESA* (United States): Michael Shlipak, Mark Sarnak, Carmen Peralta, Ronit Katz, Holly J. Kramer; *MMKD* (Austria/Germany): Florian Kronenberg, Barbara Kollerits, Eberhard Ritz; *MRC Study of Assessment of Older People* (United Kingdom): Paul Roderick, Dorothea Nitsch, Astrid Fletcher, Christopher Bulpitt; *MRFIT* (United States): Areef Ishani, James D. Neaton; *NephroTest Study* (France): Marc Froissart, Benedicte Stengel, Marie Metzger, Jean-Philippe Haymann, Pascal Houillier, Martin Flamant; *NHANES III* (United States): Brad C. Astor, Josef Coresh, Kunihiro Matsushita; *Ohasama Study* (Japan): Takayoshi Ohkubo, Hirohito Metoki, Masaaki Nakayama, Masahiro Kikuya, Yutaka Imai; *Okinawa 83/93 Cohorts* (Japan): Kunitoshi Iseki; *Pima Indian Study* (United States): Robert G. Nelson, William C. Knowler; *PREVEND* (Netherlands): Ron T. Gansevoort, Paul E. de Jong, Bakhtawar K. Mahmoodi, Hiddo J. Lambers Heerspink; *Rancho Bernardo Study* (United States): Simerjot Kaur Jassal, Elizabeth Barrett-Connor, Jaclyn Bergstrom; *RENAAL* (Netherlands/United States): Hiddo J. Lambers Heerspink, Barry E. Brenner, Dick de Zeeuw; *REGARDS* (United States): David G. Warnock, Paul Muntner, Suzanne Judd, William McClellan; *Severance Cohort Study* (Republic of Korea): Sun Ha Jee, Heejin Kimm, Jaeseong Jo, Yejin Mok, Jung Eun Lim; *STENO* (Denmark): Peter Rossing, Hans-Henrik Parving; *Sunnybrook Cohort* (Canada): Navdeep Tangri, David Naimark; *Taiwan MJ Cohort Study* (Taiwan/United States): Chi-Pang Wen, Sung-Feng Wen, Chwen-Keng Tsao, Min-Kuang Tsai; *ULSAM* (Sweden): Johan Ärnlöv, Lars Lannfelt, Anders Larsson; *ZODIAC* (Netherlands): Henk J. Bilo, Hanneke Joosten, Nanne Kleefstra, Klaas H. Groenier, Iefke Drion; *CKD-PC Steering Committee:* Brad C. Astor, Josef Coresh (chair), Ron T. Gansevoort, Brenda R. Hemmelgarn, Paul E. de Jong, Andrew S. Levey, Adeera Levin, Kunihiro Matsushita, Chi-Pang Wen, Mark Woodward; *CKD-PC Data Coordinating Center:* Shoshana H. Ballew (coordinator), Josef Coresh (principal investigator), Morgan Grams, Bakhtawar K. Mahmoodi, Kunihiro Matsushita (director), and Yingying Sang (lead programmer), Mark Woodward (senior statistician); *administrative support:* Laura Camarata, Xuan Hui, Jennifer Seltzer, Heather Winegrad.
Funding/Support: The CKD-PC Data Coordinating Center is funded in part by a program grant from the US National Kidney Foundation (National Kidney Foundation funding sources include Abbott and Amgen). A variety of sources have supported enrollment and data collection including laboratory measurements and follow-up in the collaborating cohorts of the CKD-PC. These funding sources include government agencies such as national institutes of health and medical research councils as well as foundations and industry sponsors listed in eAppendix 3.
Role of the Sponsor: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Online-Only Material: The 3 eAppendixes, 2 eTables, and 23 eFigures are available at http://www.jama.com.

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease. *Am J Kidney Dis*. 2002;39(2)(suppl 1):S1-S266.
2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007; 298(17):2038-2047.
3. Hallan SI, Coresh J, Astor BC, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol*. 2006; 17(8):2275-2284.
4. Zhang L, Zhang P, Wang F, et al. Prevalence and factors associated with CKD. *Am J Kidney Dis*. 2008; 51(3):373-384.
5. Gansevoort RT, de Jong PE. The case for using albuminuria in staging chronic kidney disease. *J Am Soc Nephrol*. 2009;20(3):465-468.
6. Hallan SI, Ritz E, Lydersen S, et al. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol*. 2009;20(5):1069-1077.
7. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease. *Kidney Int*. 2011;80(1):17-28.
8. Perk J, De Backer G, Gohlke H, et al. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012). *Eur Heart J*. 2012;33(13):1635-1701.
9. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA*. 2003;289(19):2560-2572.
10. O'Hare AM, Hailpern SM, Pavkov ME, et al. Prognostic implications of the urinary albumin to creatinine ratio in veterans of different ages with diabetes. *Arch Intern Med*. 2010;170(11):930-936.
11. Muntner P, Bowling CB, Gao L, et al. Age-specific association of reduced estimated glomerular filtration rate and albuminuria with all-cause mortality. *Clin J Am Soc Nephrol*. 2011;6(9):2200-2207.
12. Winearls CG, Glassock RJ. Classification of chronic kidney disease in the elderly. *Nephron Clin Pract*. 2011; 119(suppl 1):c2-c4.
13. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. 2007;18(10):2758-2765.
14. Glassock RJ, Rule AD. The implications of anatomical and functional changes of the aging kidney. *Kidney Int*. 2012;82(3):270-277.
15. Gansevoort RT, Matsushita K, van der Velde M, et al; CKD-PC. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. *Kidney Int*. 2011;80(1):93-104.
16. Matsushita K, van der Velde M, Astor BC, et al; CKD-PC. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts. *Lancet*. 2010; 375(9731):2073-2081.
17. van der Velde M, Matsushita K, Coresh J, et al; CKD-PC. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. *Kidney Int*. 2011;79(12):1341-1352.
18. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
19. Matsushita K, Mahmoodi BK, Woodward M, et al; CKD-PC. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*. 2012;307(18):1941-1951.
20. Levey AS, Coresh J, Greene T, et al; CKD-EPI. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007; 53(4):766-772.
21. Thompson S, Kaptoge S, White I, et al; Emerging Risk Factors Collaboration. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. *Int J Epidemiol*. 2010; 39(5):1345-1359.
22. Mitsuhashi H, Yatsuya H, Matsushita K, et al. Uric acid and left ventricular hypertrophy in Japanese men. *Circ J*. 2009;73(4):667-672.
23. Hemmelgarn BR, Clement F, Manns BJ, et al. Overview of the Alberta Kidney Disease Network. *BMC Nephrol*. 2009;10:30.
24. Matsushita K, Selvin E, Bash LD, et al. Change in estimated GFR associates with coronary heart disease and mortality. *J Am Soc Nephrol*. 2009;20(12):2617-2624.
25. White SL, Polkinghorne KR, Atkins RC, Chadban SJ. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations. *Am J Kidney Dis*. 2010;55(4):660-670.
26. Shankar A, Klein R, Klein BE. The association among

smoking, heavy drinking, and chronic kidney disease. *Am J Epidemiol*. 2006;164(3):263-271.
27. Zhang L, Zuo L, Xu G, et al. Community-based screening for chronic kidney disease among populations older than 40 years in Beijing. *Nephrol Dial Transplant*. 2007; 22(4):1093-1099.
28. Shlipak MG, Katz R, Kestenbaum B, et al. Rate of kidney function decline in older adults: a comparison using creatinine and cystatin C. *Am J Nephrol*. 2009;30 (3):171-178.
29. Shimizu Y, Maeda K, Imano H, et al. Chronic kidney disease and drinking status in relation to risks of stroke and its subtypes. *Stroke*. 2011;42(9):2531-2537.
30. Jafar TH, Qadri Z, Hashmi S. Prevalence of microalbuminuria and associated electrocardiographic abnormalities in an Indo-Asian population. *Nephrol Dial Transplant*. 2009;24(7):2111-2116.
31. Zhang QL, Koenig W, Raum E, et al. Epidemiology of chronic kidney disease. *Prev Med*. 2009;48(2): 122-127.
32. Parikh NI, Hwang S-J, Larson MG, et al. Chronic kidney disease as a predictor of cardiovascular disease (from the Framingham Heart Study). *Am J Cardiol*. 2008; 102(1):47-53.
33. Cirillo M, Lanti MP, Menotti A, et al. Definition of kidney dysfunction as a cardiovascular risk factor. *Arch Intern Med*. 2008;168(6):617-624.
34. Noda H, Iso H, Irie F, et al. Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage. *Circulation*. 2009;119 (16):2136-2145.
35. Bui AL, Katz R, Kestenbaum B, et al. Cystatin C and carotid intima-media thickness in asymptomatic adults. *Am J Kidney Dis*. 2009;53(3):389-398.
36. Roderick PJ, Atkins RJ, Smeeth L, et al. CKD and mortality risk in older people. *Am J Kidney Dis*. 2009; 53(6):950-960.
37. Astor BC, Hallan SI, Miller ER III, et al. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol*. 2008;167(10):1226-1234.
38. Nakayama M, Metoki H, Terawaki H, et al. Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population—the Ohasama study. *Nephrol Dial Transplant*. 2007;22(7):1910-1915.
39. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int*. 2003;63(4):1468-1474.
40. Iseki K, Kohagura K, Sakima A, et al. Changes in the demographics and prevalence of chronic kidney disease in Okinawa, Japan (1993 to 2003). *Hypertens Res*. 2007; 30(1):55-62.
41. Hillege HL, Fidler V, Diercks GF, et al; PREVEND Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation*. 2002;106(14):1777-1782.
42. Jassal SK, Kritz-Silverstein D, Barrett-Connor E. A prospective study of albuminuria and cognitive function in older adults. *Am J Epidemiol*. 2010;171(3):277-286.
43. Howard VJ, Cushman M, Pulley L, et al. The Reasons for Geographic and Racial Differences in Stroke Study. *Neuroepidemiology*. 2005;25(3):135-143.
44. Kimm H, Yun JE, Jo J, Jee SH. Low serum bilirubin level as an independent predictor of stroke incidence. *Stroke*. 2009;40(11):3422-3427.
45. Wen CP, Cheng TY, Tsai MK, et al. All-cause mortality attributable to chronic kidney disease. *Lancet*. 2008; 371(9631):2173-2182.
46. Ingelsson E, Sundström J, Lind L, et al. Low-grade albuminuria and the incidence of heart failure in a community-based cohort of elderly men. *Eur Heart J*. 2007; 28(14):1739-1745.
47. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial). *Lancet*. 2007;370(9590): 829-840.
48. Tonelli M, Jose P, Curhan G, et al; CARE Trial Investigators. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease. *BMJ*. 2006;332(7555):1426.
49. Jurkovitz CT, Qiu Y, Wang C, et al. The Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*. 2008; 51(4)(suppl 2):S3-S12.
50. Lee BJ, Forbes K. The role of specialists in managing the health of populations with chronic illness. *BMJ*. 2009;339:b2395.
51. Ishani A, Grandits GA, Grimm RH, et al. Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the Multiple Risk Factor Intervention Trial. *J Am Soc Nephrol*. 2006; 17(5):1444-1452.
52. Pavkov ME, Knowler WC, Hanson RL, et al. Predictive power of sequential measures of albuminuria for progression to ESRD or death in Pima Indians with type 2 diabetes. *Am J Kidney Dis*. 2008;51(5):759-766.
53. Bilo HJ, Logtenberg SJ, Joosten H, et al. Modification of diet in renal disease and Cockcroft-Gault formulas do not predict mortality (ZODIAC-6). *Diabet Med*. 2009;26(5):478-482.
54. Wright JT Jr, Bakris G, Greene T, et al; AASK Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease. *JAMA*. 2002;288(19):2421-2431.
55. Levin A, Djurdjev O, Beaulieu M, Er L. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis*. 2008;52(4):661-671.
56. Landray MJ, Thambyrajah J, McGlynn FJ, et al. Epidemiological evaluation of known and suspected cardiovascular risk factors in chronic renal impairment. *Am J Kidney Dis*. 2001;38(3):537-546.
57. Perkins RM, Bucaloiu ID, Kirchner HL, et al. GFR decline and mortality risk among patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(8):1879-1886.
58. Marks A, Black C, Fluck N, et al. Translating chronic kidney disease epidemiology into patient care—the individual/public health risk paradox [published online April 24, 2012]. *Nephrol Dial Transplant*. doi:10.1093/ndt/gfr746.
59. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*. 2004; 164(6):659-663.
60. van Zuilen AD, Blankestijn PJ, van Buren M, et al. Nurse practitioners improve quality of care in chronic kidney disease. *Neth J Med*. 2011;69(11):517-526.
61. Klahr S, Levey AS, Beck GJ, et al; MDRD Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med*. 1994;330(13):877-884.
62. Kronenberg F, Kuen E, Ritz E, et al. Lipoprotein(a) serum concentrations and apolipoprotein(a) phenotypes in mild and moderate renal failure. *J Am Soc Nephrol*. 2000;11(1):105-115.
63. Moranne O, Froissart M, Rossert J, et al; Nephro-Test Study Group. Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol*. 2009;20 (1):164-171.
64. Brenner BM, Cooper ME, de Zeeuw D, et al; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12): 861-869.
65. Jorsal A, Tarnow L, Frystyk J, et al. Serum adiponectin predicts all-cause mortality and end stage renal disease in patients with type I diabetes and diabetic nephropathy. *Kidney Int*. 2008;74(5):649-654.
66. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305(15):1553-1559.
67. Delanaye P, Weekers L, Dubois BE, et al. Outcome of the living kidney donor. *Nephrol Dial Transplant*. 2012;27(1):41-50.
68. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores. *JAMA*. 2001;286(2):180-187.
69. Krumholz HM, Seeman TE, Merrill SS, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA*. 1994;272 (17):1335-1340.
70. Martín-Ponce E, Santolaria F, Alemán-Valls MR, et al. Factors involved in the paradox of reverse epidemiology. *Clin Nutr*. 2010;29(4):501-506.
71. Rifkin DE, Katz R, Chonchol M, et al. Albuminuria, impaired kidney function and cardiovascular outcomes or mortality in the elderly. *Nephrol Dial Transplant*. 2010; 25(5):1560-1567.
72. Hallan SI, Astor BC, Romundstad S, et al. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals. *Arch Intern Med*. 2007;167(22):2490-2496.
73. Foley RN, Wang C, Snyder JJ, et al. Kidney function and risk triage in adults. *Kidney Int*. 2011;79 (1):99-111.
74. Conway B, Webster A, Ramsay G, et al. Predicting mortality and uptake of renal replacement therapy in patients with stage 4 chronic kidney disease. *Nephrol Dial Transplant*. 2009;24(6):1930-1937.
75. Van Pottelbergh G, Bartholomeeusen S, Buntinx F, Degryse J. The evolution of renal function and the incidence of end-stage renal disease in patients aged ≥50 years. *Nephrol Dial Transplant*. 2012;27(6):2297-2303.
76. National Institute for Health and Clinical Excellence. *Clinical Guideline 73: Chronic Kidney Disease: Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care.* 2008. http://www.nice.org.uk/CG073fullguideline. Accessed April 12, 2012.
77. Hemmelgarn BR, James MT, Manns BJ, et al; Alberta Kidney Disease Network. Rates of treated and untreated kidney failure in older vs younger adults. *JAMA*. 2012;307(23):2507-2515.
78. Poggio ED, Rule AD. A critical evaluation of chronic kidney disease—should isolated reduced estimated glomerular filtration rate be considered a "disease"? *Nephrol Dial Transplant*. 2009;24(3):698-700.
79. Prakash S, O'Hare AM. Interaction of aging and chronic kidney disease. *Semin Nephrol*. 2009;29 (5):497-503.
80. Cao JJ, Biggs ML, Barzilay J, et al. Cardiovascular and mortality risk prediction and stratification using urinary albumin excretion in older adults ages 68-102: the Cardiovascular Health Study. *Atherosclerosis*. 2008; 197(2):806-813.
81. Chang A, Kramer H. Should eGFR and albuminuria be added to the Framingham Risk Score?. *Nephron Clin Pract*. 2011;119(2):c171-c177.
82. Clase CM, Gao P, Tobe SW, et al; ONTARGET and TRANSCEND. Estimated glomerular filtration rate and albuminuria as predictors of outcomes in patients with high cardiovascular risk. *Ann Intern Med*. 2011; 154(5):310-318.
83. Ito H, Pacold IV, Durazo-Arvizu R, et al. The effect of including cystatin C or creatinine in a cardiovascular risk model for asymptomatic individuals. *Am J Epidemiol*. 2011;174(8):949-957.
84. Bowling CB, Inker LA, Gutiérrez OM, et al. Age-specific associations of reduced estimated glomerular filtration rate with concurrent chronic kidney disease complications. *Clin J Am Soc Nephrol*. 2011;6(12): 2822-2828.
85. Kilbride HS, Stevens PE, Eaglestone G, et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) Study and CKD-EPI (CKD Epidemiology Collaboration) Equations for estimation of GFR in the elderly [published online August 11, 2012]. *Am J Kidney Dis*. doi:10.1053/j.ajkd.2012.06.016.
86. Earley A, Miskulin D, Lamb EJ, et al. Estimating equations for glomerular filtration rate in the era of creatinine standardization. *Ann Intern Med*. 2012;156 (11):785-795.

