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

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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 m² vs 80 mL/min/1.73 m² 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.

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

| | | | 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[34],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.

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

| | | | 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.