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Conversion of urine protein-creatinine ratio or urine dipstick to urine albumin-creatinine ratio for use in CKD screening and prognosis: An individual participant-based meta-analysis

[Keiichi Sumida](#)^{1,*}, [Girish N Nadkarni](#)^{2,*}, [Morgan E Grams](#)³, [Yingying Sang](#)⁴, [Shoshana H Ballew](#)⁵, [Josef Coresh](#)⁶, [Kunihiro Matsushita](#)⁷, [Aditya Surapaneni](#)⁸, [Nigel Brunskill](#)⁹, [Steve J Chadban](#)¹⁰, [Alex R Chang](#)¹¹, [Massimo Cirillo](#)¹², [Kenn B Daratha](#)¹³, [Ron T Gansevoort](#)¹⁴, [Amit X Garg](#)¹⁵, [Licia Iacoviello](#)¹⁶, [Takamasa Kayama](#)¹⁷, [Tsuneo Konta](#)¹⁸, [Csaba P Kovesdy](#)¹⁹, [James Lash](#)²⁰, [Brian J Lee](#)²¹, [Rupert Major](#)²², [Marie Metzger](#)²³, [Katsuyuki Miura](#)²⁴, [David MJ Naimark](#)²⁵, [Robert G Nelson](#)²⁶, [Simon Sawhney](#)²⁷, [Nikita Stempniewicz](#)²⁸, [Mila Tang](#)²⁹, [Raymond R Townsend](#)³⁰, [Jamie P Traynor](#)³¹, [Jose M Valdivielso](#)³², [Jack Wetzels](#)³³, [Kevan R Polkinghorne](#)^{34,†}, [Hiddo JL Heerspink](#)^{35,†}, CKD

Prognosis Consortium

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Abstract

Background:

Albuminuria is the preferred measure for definition and staging of chronic kidney disease (CKD), but total urine protein or dipstick protein is often measured instead.

Objective:

To develop equations for the conversion of urine protein-to-creatinine ratio (PCR) and dipstick protein to urine albumin-to-creatinine ratio (ACR) and test their diagnostic accuracy in CKD screening and staging.

Design:

Individual participant-based meta-analysis.

Setting:

12 research cohorts and 21 clinical cohorts.

Participants:

919,383 adults with same-day measures of ACR and PCR or dipstick protein.

Measurements:

Equations to convert urine PCR and dipstick protein to ACR were developed and tested for purposes of CKD screening (ACR ≥ 30 mg/g) and staging (A2: ACR 30-299 mg/g; A3: ≥ 300 mg/g).

Results:

Median ACR was 14 mg/g (25th to 75th percentile of cohorts 5-25). The association between PCR and ACR was inconsistent for values of PCR < 50 mg/g. For higher values of PCR, the PCR conversion equations demonstrated moderate sensitivity (91%; 75%; 87%) and specificity (87%; 89%; 98%) for screening (ACR > 30 mg/g) and classification into stages A2 and A3, respectively. Urine dipstick categories of trace or greater, trace/+, and ++ for screening for ACR > 30 mg/g and classification into stages A2 and A3, respectively, had moderate sensitivity (62%; 36%; 78%) and high specificity (88%; 88%; 98%). For individual risk prediction, the estimated 2-year 4-variable kidney failure risk equation using predicted ACR from PCR had similar discrimination compared to that using observed ACR.

Limitations:

Diverse methods of ACR and PCR quantification; not necessarily the same urine sample.

Conclusion:

Urine ACR is the preferred measure of albuminuria; however, when ACR is not available, predicted ACR from PCR or urine dipstick protein may help in CKD screening, staging, and prognosis.

Primary Funding Source:

Introduction

Increased levels of urinary proteins predict adverse kidney and cardiovascular outcomes in various populations and settings.(1-5) Albumin is the most abundant protein in the urine in most types of proteinuric kidney disease, and its laboratory assay has recently been standardized.(6, 7) Thus, measurement of albuminuria is considered the gold standard when quantifying urinary protein. Clinical practice guidelines recommend screening for and monitoring of albuminuria and incorporate increased albuminuria into the definition and staging of chronic kidney disease (CKD).(8-12) In addition, several tools for assessing absolute risk of end-stage kidney disease, cardiovascular disease, and death require albuminuria as an input.(13-16)

Rather than measuring albuminuria, many providers and research studies quantify urinary protein using a total protein assay or semi-quantitative urine dipstick. These methods may be used due to lower cost, tradition, or other considerations; however, they are likely less precise than those that directly measure urine albumin. Total protein assays are not standardized and may have variable sensitivity for different protein components.(17) Dipstick protein measures provide only a gross categorization of urine protein levels.(17) Furthermore, whereas urine protein and urine albumin tests typically quantify a 24-hour collection, or are standardized to urine creatinine to estimate 24-hour excretion, dipstick protein measures are obtained at a single time point and do not correct for dilution.

The Kidney Disease Improving Global Outcomes (KDIGO) guideline notes that where albuminuria measurement is not available, urine reagent strip results can be substituted, with dipstick protein values of “trace to +” and “+ or greater” assigned to albuminuria categories 30-299 mg/g and ≥ 300 mg/g, respectively.(12) Similarly, PCR values of 150-500 mg/g and > 500 mg/g can be assigned to the respective albuminuria categories.(12) Single studies have examined the relationship between urine protein-to-creatinine ratio (PCR) or urine dipstick protein categories and urine albumin-to-creatinine ratio (ACR). (12, 18-28) However, the diagnostic performance of these thresholds and the consistency of relationships across multiple cohorts and health systems has not been established. The aim of this study was to develop equations for the conversion of urine PCR and dipstick protein to ACR and to evaluate their performance for use in efforts to screen for, categorize, and risk stratify patients with CKD.

Methods

Participating cohorts

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) includes study cohorts from around the world containing information on kidney measures. CKD-PC design has been described previously,(29) but in brief, cohorts were initially identified using a literature search in 2009 using key search terms. The consortium continues to grow and remains open (criteria for joining, ckcpc.org [↗](#)). The selection of cohorts for this paper is described in [Appendix 1](#). For this paper, cohorts are categorized based on whether they contain information primarily on participants with data collected from the structured research cohort visits or as part of clinical care

([Appendix 1](#)).⁽²⁹⁾ For the current study, cohorts were included if they contained at least 200 participants with measures of ACR and PCR or dipstick protein on the same day, and if they contained a full range of ACR values (both <300 mg/g and ≥ 300 mg/g). There was no restriction on type of cohort; and thus, included cohorts could be prospective studies, clinical trials, or administrative healthcare datasets. Similarly, there was no restriction on type of laboratory assay. All analyses in the present study were restricted to participants aged 18 years or older. This study was approved for use of de-identified data by the institutional review board at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. The need for informed consent was waived by the institutional review board.

Procedures

The methods of urine collection to assess ACR, PCR, and urine dipstick varied by eligible cohort, including collections of morning spot urine, random spot urine, and 24-hour urine ([Appendix 1](#)). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.⁽³⁰⁾ In cohorts where the creatinine measurement was not standardized to isotope dilution mass spectrometry, values were multiplied by 0.95 before eGFR calculation.⁽³¹⁾ We defined diabetes as fasting glucose ≥ 7.0 mmol/L (126 mg/dL), non-fasting glucose ≥ 11.1 mmol/L (200 mg/dL), hemoglobin A1c $\geq 6.5\%$, use of glucose lowering drugs, or self-reported diabetes. Hypertension was defined as blood pressure $>140/90$ mm Hg or the use of anti-hypertensive medications. Participants with a history of myocardial infarction, coronary revascularization, heart failure, or stroke were considered to have a history of cardiovascular disease.

Statistical Analysis

Model Development

Within each cohort, the relationships between ACR and PCR were modeled using multivariable-adjusted linear regression models ([Appendix 1](#)). After fitting models in each cohort, relationships were visually depicted to demonstrate inter-cohort variation. Given little heterogeneity, a multivariate random-effects meta-analysis using the restricted maximum likelihood for estimation and inputs of point estimates and variances for each cohort was performed using the Stata command `mvmeta`.⁽³²⁾ A similar procedure was followed for urine dipstick protein, which was categorized as negative, trace, +, ++, or >++. In sensitivity analyses, we also evaluated the associations between measures from urine samples collected within 90 days of each other.

Model Testing

Predicted levels of ACR and the prediction interval (5th-95th percentile) were calculated based on the crude and adjusted models for all combinations of sex, diabetes, and hypertension ([Appendix 1](#)). To evaluate the real-world utility of the prediction equations, we evaluated the sensitivity, specificity, and positive and negative predictive values of PCR thresholds for screening for CKD (ACR ≥ 30 mg/g) and categorizing ACR 30 to 299 mg/g (CKD stage A2) and ACR ≥ 300 mg/g (CKD stage A3). For the crude model, we used a single threshold for all participants; for the adjusted model, we varied the threshold to be the level of PCR that corresponded to

predicted ACR 30 mg/g and 300 mg/g for each combination of sex, diabetes, and hypertension. For urine dipstick protein, we evaluated the trace and greater, trace/+ category, and ++ category for CKD screening and staging, respectively. Sensitivity, specificity, and positive and negative predictive values were summarized across cohorts using the inter-cohort median and interquartile range. Sensitivity and specificity were meta-analyzed using the Stata command `metandi`, fitting a two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives conditional on the sensitivity and specificity in each study, and a bivariate normal model with the logit transforms of sensitivity and specificity across studies. (33) Analyses were also performed in subgroups of sex, eGFR, diabetes, and hypertension.

Among participants with eGFR <60 mL/min/1.73 m², in cohorts that supplied data on serum creatinine and same-day PCR and ACR, we plotted the 2-year, 4-variable kidney failure risk equation (KFRE) using predicted ACR versus that using observed ACR. (13, 34) We evaluated sensitivity, specificity, and positive and negative predictive value for the clinical thresholds of 20% and 40% 2-year risk of kidney failure separately in cohorts sending data to the Data Coordinating Center and in the 12 OptumLabs®Data Warehouse (OLDW) cohorts. Finally, we compared the discrimination of the KFRE using predicted ACR to that using observed ACR in those cohorts with data on end-stage kidney disease outcomes.

All analyses were performed in Stata 15 (StataCorp. 2017. College Station, TX: StataCorp LLC). Statistical significance was determined using a two-sided test with a threshold p-value of <0.05.

Role of the Funding Source

The funders had no role in the study design, data collection, analysis, data interpretation, or writing of the report. MEG and JC had full access to all analyses and all authors had final responsibility for the decision to submit for publication, informed by discussions with collaborators.

Results

Participant characteristics

The study included 919,383 participants in 33 cohorts, including 12 research cohorts (n = 36,592), 21 clinical cohorts (n = 882,791), with data collected between 1982 and 2019 (Table 1). Overall, mean age was 61 years (SD 15); 50% were female; 4.8% were black; 56% had diabetes; and 72% had hypertension. Among the 919,383 participants, there were 147,066 pairs of ACR and PCR tests, and 1,903,359 pairs of ACR and urine dipstick tests. The median ACR was 14 mg/g (25th and 75th percentile of cohorts, 5-25); median PCR was 197 mg/g (89-682); and 7.0% of urine dipstick tests indicated presence of trace proteins, 3.9% of +, 1.8% of ++, and 2.2% of > ++ (Table 1, Supplemental Table 1).

Table 1.

Baseline characteristics in participants with PCR or dipstick in measurements on the same day as the urine ACR measure; random visit was selected if multiple measurements per person

Study	N	Cohort type	Age (SD), y	ACR (25th to 75th percentile of cohorts), mg/g	eGFR (SD), ml/min/1.73m ²	eGFR <60, N (%)	Female, %	DM, %	HTN, %
AusDiab	11204	research	55 (15)	5 (4-9)	84 (17)	944 (8%)	55	9.7	36
CanPREDDICT	2648	research	68 (13)	141 (27-769)	27 (10)	2236 (100%)	37	49	97
CRIC	3772	research	58 (11)	51 (8-449)	45 (15)	3200 (85%)	45	48	88
IDNT	1706	research	60 (8)	1380 (586-2682)	50 (19)	1166 (72%)	34	100	100
MASTERPLAN	516	research	61 (12)	77 (16-344)	36 (16)	479 (93%)	31	44	95
NIPPON DATA2010	2796	research	59 (16)	6 (3-18)	97 (17)	77 (3%)	57	13	36
Nefrona	274	research	59 (13)	184 (34-659)	33 (17)	241 (90%)	39	30	98
NephroTest	1677	research	60 (15)	83 (14-451)	43 (22)	1341 (80%)	33	30	92
Pima	6081	research	38 (15)	13 (7-38)	115 (21)	192 (3%)	58	37	28
RENAAL	722	research	61 (7)	1013 (375-2287)	42 (14)	617 (88%)	38	100	100
SUN-Macro	896	research	63 (9)	1405 (663-2516)	33 (11)	840 (99%)	23	100	100
Takahata	4300	research	64 (10)	9 (6-18)	97 (13)	65 (2%)	55	9.3	62

Study	N	Cohort type	Age (SD), y	ACR (25th to 75th percentile of cohorts), mg/g	eGFR (SD), ml/min/1.73m ²	eGFR <60, N (%)	Female, %	DM, %	HTN, %
CURE-CKD	429	clinical	61 (18)	51 (11-223)	59 (32)	226 (58%)	48	26	52
Geisinger	3128	clinical	67 (15)	35 (9-221)	51 (25)	2195 (73%)	52	67	95
ICES-KDT	589989	clinical	60 (16)	14 (5-25)	83 (23)	97253 (17%)	50	54	71
LCC	7384	clinical	77 (10)	10 (4-35)	50 (13)	5821 (79%)	59	51	96
Mt_Sinai_BioMe	1679	clinical	61 (15)	61 (11-524)	49 (26)	1123 (70%)	48	49	79
OLDW cohort 1	16341	clinical	62 (14)	16 (7-41)	75 (24)	4140 (27%)	52	75	82
OLDW cohort 2	16396	clinical	64 (14)	16 (7-52)	74 (26)	4906 (31%)	50	84	85
OLDW cohort 3	30940	clinical	60 (15)	9 (5-27)	81 (23)	5571 (18%)	52	47	64
OLDW cohort 4	57673	clinical	63 (14)	16 (7-49)	75 (25)	15407 (28%)	52	69	74
OLDW cohort 5	27204	clinical	59 (15)	21 (7-45)	80 (28)	6596 (25%)	53	76	82
OLDW cohort 6	2318	clinical	62 (15)	16 (7-63)	71 (27)	774 (35%)	53	73	85
OLDW cohort 7	12226	clinical	66 (13)	12 (6-35)	72 (23)	3803 (31%)	50	74	82
OLDW cohort 8	8083	clinical	62 (15)	15 (6-60)	75 (25)	2230 (29%)	51	71	80
OLDW cohort 9	3971	clinical	58 (14)	13 (6-31)	82 (25)	753 (20%)	48	57	71
OLDW cohort 10	26396	clinical	61 (15)	11 (5-35)	80 (24)	5098 (20%)	51	58	69

Study	N	Cohort type	Age (SD), y	ACR (25th to 75th percentile of cohorts), mg/g	eGFR (SD), ml/min/1.73m ²	eGFR <60, N (%)	Female, %	DM, %	HTN, %
OLDW cohort 11	53960	clinical	61 (14)	12 (5-45)	76 (25)	13925 (27%)	46	53	70
OLDW cohort 12	7942	clinical	60 (15)	11 (5-45)	79 (27)	1853 (24%)	53	65	75
PSP-CKD	1253	clinical	76 (10)	18 (6-53)	50 (16)	503 (73%)	52	45	83
RCAV	9361	clinical	66 (11)	13 (6-56)	72 (20)	2436 (28%)	3.6	81	92
Sunnybrook	2043	clinical	58 (18)	82 (16-391)	59 (32)	1135 (56%)	49	40	67
West of Scotland	4075	clinical	67 (14)	19 (4-95)	33 (19)	3766 (92%)	46	35	42
Total	919383		61 (15)	14 (5-25)	80 (25)	190912 (21%)	50	56	72

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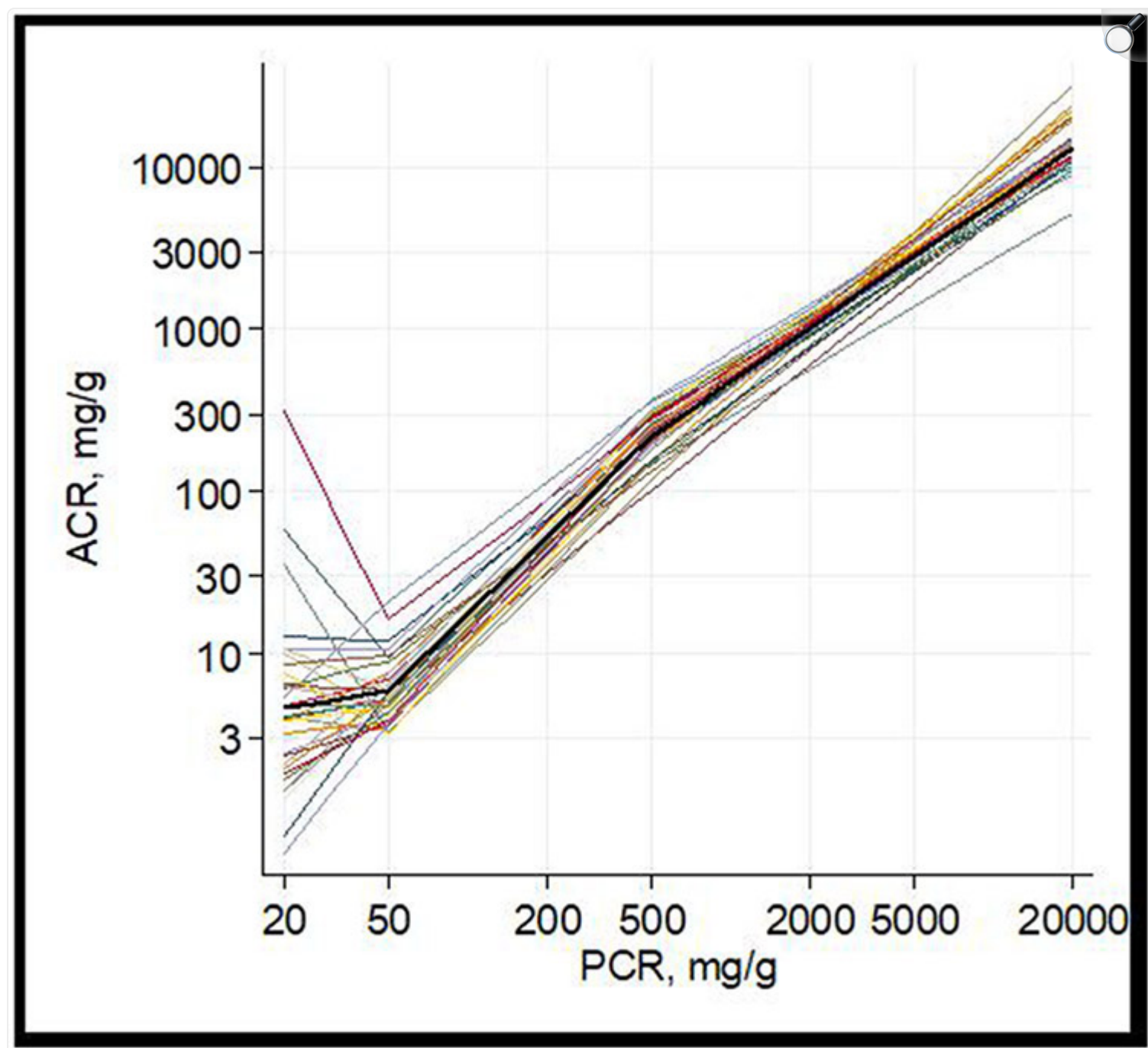
Cohort type indicates if data was collected as part of structured research cohort visits or as part of clinical care. Cohort abbreviations are detailed in [Appendix 2](#). SD: standard deviation; DM: diabetes mellitus; HTN: hypertension

Relationship between PCR and ACR and urine dipstick category and ACR

For values of PCR >50 mg/g, the relationship between PCR and ACR was nearly linear on the log scale, with a shallower slope for values of PCR >500 mg/g compared to PCR 50-500 mg/g and relative consistency across cohorts ([Figure 1](#), [Supplemental Figure 1](#), [Supplemental Table 2](#)). Below PCR 50 mg/g, there was little consistent association across cohorts. Using the crude model, there was a 2.99-fold increase in predicted ACR for each doubling of PCR in the range of 50-500 mg/g, and 2.18-fold increase in predicted ACR for each doubling of PCR ≥500 mg/g. In the adjusted model, the respective increase in predicted ACR for changes in PCR was similar (2.96-fold and 2.16-fold), and the effects of sex, diabetes, and hypertension on the relationship were relatively small ([Supplemental Table 3](#)). The relationship between PCR and ACR remained highly similar across all

combinations of sex, diabetes, and hypertension status ([Supplemental Figure 2](#)). The meta-analyzed associations between PCR and ACR were also similar when using values measured within 90 days ([Supplemental Table 4](#)).

Figure 1.



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Relationship between urine protein-to-creatinine (PCR) and urine albumin-to-creatinine (ACR) values in individual cohorts (multicolored lines) and after random effects meta-analysis (thick black line) in the crude model

Associations were estimated using log-transformed urine albumin-to-creatinine ratio (ACR) and urine protein-to-creatinine ratio (PCR), with the latter modeled using linear splines with knots at 50 mg/g and 500 mg/g.

There was a graded relationship between urine dipstick protein categories and ACR, with some heterogeneity across cohorts ([Supplemental Figure 3](#); [Supplemental Table 5A](#)). The relationship between dipstick category and ACR remained largely similar in the adjusted model, with relatively small effects of sex, diabetes, and hypertension ([Supplemental Table 5B](#)). The relationship between dipstick and ACR was also similar when using all values measured within 90 days ([Supplemental Table 6](#)).

Prediction model performance

The prediction equations for the conversion of PCR to ACR and urine dipstick protein categories to ACR based on meta-analyzed associations of same-day measures as well as the equations for predicted error are shown in [Table 2](#). Scatter plots of observed compared to predicted ACR showed closer approximation in the higher compared to lower levels in most cohorts ([Supplemental Figure 4](#)). Predicted ACR values and their 95% prediction intervals (incorporating both standard error and predicted error, interpreted as the interval in which 95% chance that a concomitantly measured ACR would fall into that interval) for a variety of levels of PCR and dipstick categories are shown in [Table 3](#) and [Supplemental Table 7](#), respectively. The predicted ACR levels corresponding to PCR 150 mg/g and 500 mg/g were 33 mg/g (95% prediction interval: 12 to 90) and 220 mg/g (prediction interval 113 to 427 mg/g) respectively, in the crude model. Thresholds of the PCR levels corresponding to predicted ACR 30 mg/g and 300 mg/g used to test performance were 142 mg/g and 660 mg/g, respectively. The predicted values of ACR for trace, +, ++, and > ++ dipstick protein were 25 mg/g (95% prediction interval, 8-80), 67 mg/g (21-207), 337 mg/g (132-860), and 1229 mg/g (734-2057), respectively. A tool for converting PCR or dipstick values to ACR is available at ckdpcrisk.org/pcr2acr [↗](#).

Table 2.

Equations for the conversion of urine protein-to-creatinine (PCR) to urine albumin-to-creatinine (ACR) and urine dipstick protein to urine ACR from the crude and adjusted models, in mg/g

PCR equations		
Crude model	Predicted ACR	$pACR = \exp(5.3920 + 0.3072 \times \log(\min(PCR/50, 1)) + 1.5793 \times \log(\max(\min(PCR/500, 1), 0.1)) + 1.1266 \times \log(\max(PCR/500, 1)))$
	Predicted error	$pErr = \sqrt{\exp(-2.2996 + 0.1043 \times \log(\min(pACR/30, 1)) - 0.4401 \times \log(\max(\min(pACR/300, 1), 0.1)) - 0.3897 \times \log(\max(pACR/300, 1)))}$
Adjusted model	Predicted ACR	$pACR = \exp(5.2659 + 0.2934 \times \log(\min(PCR/50, 1)) + 1.5643 \times \log(\max(\min(PCR/500, 1), 0.1)) + 1.1109 \times \log(\max(PCR/500, 1)) - 0.0773 \times (\text{if female}) + 0.0797 \times (\text{if diabetic}) + 0.1265 \times (\text{if hypertensive}))$
	Predicted error	$pErr = \sqrt{\exp(-2.0664 + 0.1658 \times \log(\min(pACR/30, 1)) - 0.4599 \times \log(\max(\min(pACR/300, 1), 0.1)) - 0.3084 \times \log(\max(pACR/300, 1)) + 0.0847 \times (\text{if female}) - 0.2553 \times (\text{if diabetic}) - 0.2299 \times (\text{if hypertensive}))}$
Dipstick equations		
Crude model	Predicted ACR	$pACR = \exp(2.4738 + 0.7539 \times (\text{if trace}) + 1.7243 \times (\text{if +}) + 3.3475 \times (\text{if ++}) + 4.6399 \times (\text{if > ++}))$
	Predicted error	$pErr = \sqrt{\exp(-1.3710 + 0.6843 \times \log(\min(pACR/30, 1)) - 0.1869 \times \log(\max(\min(pACR/300, 1), 0.1)) - 0.9220 \times \log(\max(pACR/300, 1)))}$
Adjusted model	Predicted ACR	$pACR = \exp(2.0373 + 0.7270 \times (\text{if trace}) + 1.6775 \times (\text{if +}) + 3.2622 \times (\text{if ++}) + 4.5435 \times (\text{if > ++}) + 0.0822 \times (\text{if female}) + 0.27249 \times (\text{if diabetic}) + 0.33627 \times (\text{if hypertensive}))$
	Predicted error	$pErr = \sqrt{\exp(-0.4525 + 0.5939 \times \log(\min(pACR/30, 1)) - 0.1292 \times \log(\max(\min(pACR/300, 1), 0.1)) - 0.2610 \times \log(\max(pACR/300, 1)) - 0.0772 \times (\text{if female}) - 0.2093 \times (\text{if diabetic}) - 0.1624 \times (\text{if hypertensive}))}$

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Diabetes as fasting glucose ≥ 7.0 mmol/L (126 mg/dL), non-fasting glucose ≥ 11.1 mmol/L (200 mg/dL), hemoglobin A1c $\geq 6.5\%$, use of glucose lowering drugs, or self-reported diabetes.

Hypertension was defined as blood pressure >140/90 mm Hg or the use of anti-hypertensive medications. Log refers to the natural log-transformation (ln).

Prediction interval

$$\exp(\log(\text{pACR}) - 1.96 \times \text{pErr})$$

$$\exp(\log(\text{pACR}) + 1.96 \times \text{pErr})$$

Table 3.

Predicted urine albumin-to-creatinine (ACR) values and their prediction intervals for a variety of levels of urine protein-to-creatinine (PCR) from the crude and adjusted equations, in mg/g

PCR (mg/g [*])	Crude Model ACR (mg/g [*])	Adjusted Model							
		ACR (mg/g [*])							
		Male				Female			
		No HTN		HTN		No HTN		HTN	
		No DM	DM	No DM	DM	No DM	DM	No DM	DM
50	6 (2-15)	5 (2-15)	6 (2-14)	6 (2-15)	6 (3-15)	5 (2-14)	5 (2-14)	6 (2-14)	6 (3-14)
150	33 (12-90)	29 (9-96)	32 (11-89)	33 (12-94)	36 (15-88)	27 (8-93)	30 (10-87)	31 (10-92)	33 (13-86)
500	220 (113-427)	194 (90-419)	210 (108-408)	220 (113-428)	238 (134-424)	179 (79-407)	194 (96-394)	203 (100-413)	220 (119-407)
700	321 (174-592)	281 (139-571)	305 (165-562)	319 (172-591)	346 (202-591)	260 (123-552)	282 (147-540)	296 (154-567)	320 (182-563)
1000	480 (272-845)	418 (216-811)	453 (255-806)	475 (266-847)	514 (311-850)	387 (192-779)	419 (228-770)	439 (238-810)	476 (280-810)
2000	1047 (644-1703)	903 (501-1627)	978 (586-1632)	1025 (613-1714)	1110 (710-1736)	836 (449-1556)	905 (528-1554)	949 (551-1633)	1027 (641-1648)
3000	1653 (1059-2580)	1417 (818-2454)	1535 (952-2474)	1608 (995-2599)	1742 (1147-2643)	1312 (735-2342)	1421 (858-2351)	1488 (897-2471)	1612 (1038-2504)
5000	2940 (1975-4376)	2499 (1511-4133)	2707 (1748-4192)	2836 (1827-4403)	3072 (2096-4502)	2314 (1360-3935)	2506 (1579-3976)	2625 (1650-4177)	2843 (1899-4257)

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*Conversion factor for transforming units from mg/g to mg/mmol: divide by 8.84 mmol/g.

The prediction interval was estimated as the predicted level of ACR ± 1.96 times the square root of the addend of the squared standard error term and the squared predicted error. DM: diabetes mellitus; HTN: hypertension.

Diagnostic test accuracy: Screening for CKD

The sensitivity, specificity, positive predictive value, and negative predictive value of the predicted ACR using the PCR conversion equation for detecting ACR ≥ 30 mg/g (i.e., CKD screening) varied by cohort but were similar between crude and adjusted models ([Supplemental Table 8](#)). In the crude model, meta-analyzed sensitivity and specificity of the PCR-based equation for detecting ACR ≥ 30 mg/g were 91.2% [95% CI 87.3-93.9] and 86.5% [81.4-90.3], respectively; and pooled median positive and negative predictive values were 91.1% [25th to 75th percentile of cohorts 87.5-94.5] and 84.5% [77.6-89.4], respectively ([Table 4A](#), [Supplemental Table 8](#)).

Table 4.

Crude model sensitivity and specificity for detecting different levels of urine albumin-to-creatinine (ACR) from equivalent urine protein-to-creatinine (PCR) levels (A) or dipstick categories (B), overall and in subgroups

A	N	ACR ≥30 mg/g		ACR 30-299 mg/g		ACR ≥300 mg/g	
		PCR ≥142 mg/g		PCR 142-660 mg/g		PCR ≥660 mg/g	
		Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Overall	147066	0.912 (0.873, 0.939)	0.865 (0.814, 0.903)	0.749 (0.708, 0.787)	0.887 (0.863, 0.907)	0.866 (0.835, 0.892)	0.975 (0.962, 0.983)
Male	87621	0.914 (0.875, 0.941)	0.880 (0.831, 0.916)	0.755 (0.710, 0.794)	0.891 (0.867, 0.911)	0.858 (0.827, 0.885)	0.977 (0.964, 0.985)
Female	59445	0.910 (0.871, 0.939)	0.851 (0.798, 0.892)	0.739 (0.699, 0.775)	0.886 (0.858, 0.909)	0.881 (0.847, 0.908)	0.975 (0.962, 0.983)
No Diabetes	71124	0.871 (0.828, 0.904)	0.889 (0.849, 0.920)	0.711 (0.667, 0.751)	0.878 (0.848, 0.902)	0.826 (0.791, 0.856)	0.981 (0.969, 0.988)
Diabetes	74757	0.929 (0.900, 0.950)	0.852 (0.795, 0.895)	0.775 (0.742, 0.804)	0.884 (0.863, 0.902)	0.882 (0.853, 0.906)	0.970 (0.957, 0.979)
No Hypertension	37030	0.856 (0.806, 0.895)	0.909 (0.872, 0.936)	0.678 (0.626, 0.727)	0.896 (0.865, 0.920)	0.932 (0.785, 0.871)	0.980 (0.966, 0.989)
Hypertension	108656	0.919 (0.884, 0.944)	0.856 (0.803, 0.897)	0.759 (0.719, 0.795)	0.882 (0.859, 0.902)	0.870 (0.839, 0.896)	0.974 (0.961, 0.982)
CKD stage G1-2	61299	0.863 (0.819, 0.898)	0.911 (0.878, 0.936)	0.733 (0.685, 0.775)	0.889 (0.863, 0.910)	0.818 (0.778, 0.853)	0.987 (0.979, 0.992)
CKD stage G3	44032	0.918 (0.876, 0.947)	0.826 (0.740, 0.888)	0.752 (0.714, 0.787)	0.876 (0.851, 0.898)	0.860 (0.820, 0.892)	0.974 (0.960, 0.983)
CKD stage G4-5	28174	0.960 (0.943,	0.728 (0.637,	0.755 (0.717,	0.881 (0.853,	0.924 (0.900,	0.916 (0.873,

A	N	ACR ≥30 mg/g		ACR 30-299 mg/g		ACR ≥300 mg/g	
		PCR ≥142 mg/g		PCR 142-660 mg/g		PCR ≥660 mg/g	
		Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
		0.971)	0.803)	0.790)	0.905)	0.942)	0.945)

B	N	ACR ≥30 mg/g		ACR 30-299 mg/g		ACR ≥300 mg/g	
		By dipstick trace or more		By dipstick trace or +		By dipstick ++ or more	
		Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Overall	1903359	0.620 (0.509, 0.720)	0.878 (0.833, 0.912)	0.356 (0.296, 0.421)	0.882 (0.843, 0.913)	0.776 (0.717, 0.826)	0.975 (0.955, 0.986)
Male	974381	0.663 (0.559, 0.753)	0.875 (0.831, 0.909)	0.385 (0.319, 0.456)	0.881 (0.842, 0.911)	0.803 (0.745, 0.851)	0.971 (0.948, 0.984)
Female	928978	0.569 (0.453, 0.678)	0.880 (0.834, 0.915)	0.328 (0.272, 0.390)	0.883 (0.843, 0.914)	0.742 (0.682, 0.794)	0.974 (0.958, 0.984)
No Diabetes	689075	0.611 (0.490, 0.720)	0.873 (0.826, 0.909)	0.353 (0.283, 0.429)	0.881 (0.837, 0.914)	0.775 (0.719, 0.823)	0.979 (0.961, 0.989)
Diabetes	1213978	0.631 (0.524, 0.726)	0.876 (0.833, 0.910)	0.359 (0.301, 0.421)	0.880 (0.845, 0.909)	0.783 (0.723, 0.832)	0.970 (0.948, 0.983)
No Hypertension	449679	0.583 (0.460, 0.698)	0.873 (0.822, 0.911)	0.356 (0.297, 0.420)	0.881 (0.838, 0.914)	0.758 (0.696, 0.811)	0.983 (0.965, 0.992)
Hypertension	1453584	0.628 (0.523, 0.723)	0.877 (0.833, 0.911)	0.360 (0.299, 0.426)	0.881 (0.843, 0.911)	0.785 (0.727, 0.834)	0.971 (0.947, 0.984)
CKD stage G1-2	1431248	0.578 (0.469, 0.680)	0.881 (0.838, 0.914)	0.366 (0.310, 0.425)	0.884 (0.946, 0.913)	0.720 (0.693, 0.746)	0.983 (0.972, 0.990)
CKD stage G3	346405	0.656 (0.550, 0.748)	0.869 (0.826, 0.902)	0.377 (0.312, 0.478)	0.873 (0.836, 0.902)	0.799 (0.746, 0.844)	0.967 (0.944, 0.981)
CKD stage G4-5	80529	0.800 (0.716,	0.840 (0.784,	0.389 (0.306,	0.870 (0.825,	0.852 (0.809,	0.940 (0.900,

A	N	ACR ≥ 30 mg/g		ACR 30-299 mg/g		ACR ≥ 300 mg/g	
		PCR ≥ 142 mg/g		PCR 142-660 mg/g		PCR ≥ 660 mg/g	
		Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
		0.864)	0.884)	0.480)	0.904)	0.887)	0.964)

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The sensitivity, specificity, positive predictive value, and negative predictive value for urine dipstick categories of trace and greater for ACR ≥ 30 mg/g varied across cohorts ([Supplemental Table 9](#)). The meta-analyzed sensitivity and specificity of the urine dipstick trace and greater for detecting ACR ≥ 30 mg/g were 62.0% [95% CI 50.9-72.0] and 87.8% [83.3-91.2], respectively; and pooled median positive and negative predictive values were 70.8% [25th to 75th percentile of cohorts 65.8-73.6] and 81.7% [77.6-85.2], respectively ([Table 4B](#), [Supplemental Table 9](#)).

Diagnostic test accuracy: CKD staging

The sensitivity and specificity value of the crude PCR conversion equation for identifying CKD stage A2 (ACR 30-299 mg/g) was 74.9% [95% CI 70.8-78.7], 88.7% [86.3-90.7], respectively; and positive and negative predictive values were 72.5% [25th to 75th percentile of cohorts 69.2-75.6] and 88.7% [86.0-91.1], respectively ([Table 4A](#), [Supplemental Table 10](#)). The equations had slightly higher sensitivity and higher specificity for detecting A3 (ACR ≥ 300 mg/g), with meta-analyzed sensitivity and specificity of 86.6% [95% CI 83.5-89.2] and 97.5% [96.2-98.3], respectively, and pooled median positive and negative predictive values of 90.4% [25th to 75th percentile of cohorts 88.3-94.8] and 95.1% [91.5-97.5]. Performance was similar using the adjusted equation ([Table 4A](#), [Supplemental Table 10](#) and [11](#)).

Dipstick values of trace/+ had lower sensitivity and specificity for CKD stage A2 ([Table 4B](#), [Supplemental Table 12](#)). Dipstick values of ++ had meta-analyzed sensitivity and specificity of 77.6% [95% CI 71.7-82.6] and 97.5% [95.5-98.6], respectively, for CKD stage A3 ([Table 4B](#), [Supplemental Table 13](#)). Diagnostic performance was highly similar by subgroup of sex, diabetes, hypertension, and CKD G-stage ([Table 4B](#)).

Diagnostic test accuracy: CKD prognosis

The kidney failure risk estimates calculated by the 2-year 4-variable KFRE using predicted ACR versus that using observed ACR showed agreement, particularly in the OLDW cohorts ([Supplemental Figure 5](#)). The sensitivity and specificity for the 2-year 40% kidney failure risk threshold were 80.5% and 99.6%, respectively, using the crude model in cohorts that sent data to the Data Coordinating Center and 95.6% and 99.4%, respectively, in the OLDW cohorts. The median (25th to 75th percentile of cohorts) C-statistic for the 2-year KFRE across cohorts was 0.879 [IQI 0.842, 0.907] using observed ACR, 0.883 [0.844, 0.909] using ACR predicted with the crude equation, and 0.883 [0.845, 0.909] using ACR predicted using the adjusted equation. The C-statistic using

predicted compared to observed ACR was statistically worse in only two out of 25 cohorts ([Supplemental Table 14](#)).

Discussion

In this international collaborative meta-analysis of 919,383 participants from 33 cohorts, we found a consistent overall relationship between PCR and ACR for PCR >50 mg/g and between urine dipstick protein categories and ACR across a wide range of cohorts. We developed equations for the conversion of PCR or urine dipstick protein categories to ACR, and evaluated the equations for potential use in individual screening and classification efforts and risk prediction. For efforts to categorize patients into CKD stages A2 and A3, the PCR conversion equations demonstrated moderate sensitivity and specificity (>74%) for the detection of ACR 30-299 mg/g and ≥ 300 mg/g; the urine dipstick trace/+ and ++ categories had high specificity (>88%) but lower sensitivity (<78%) for identifying ACR 30-299 mg/g and ≥ 300 mg/g, respectively. For individual risk prediction, the estimated 2-year 4-variable KFRE using predicted ACR was highly comparable to that using observed ACR.

Our empirically developed equation for the conversion of PCR to ACR corresponded well with threshold estimates in the current KDIGO guideline on CKD staging.[\(12\)](#) The guideline recommends use of ACR for defining and staging CKD, with ACR values of 30 mg/g and 300 mg/g defining albuminuria categories A2 and A3, respectively. Our crude equation suggests that a “trace” value on urine dipstick corresponds to an ACR of 25 mg/g, “+” corresponds to a value of 67 mg/g, and “++” corresponds to a value of 337 mg/g. Similarly, we estimate in the crude PCR equation that a PCR value of 150 mg/g corresponds to an ACR value of 33 mg/g, albeit with a prediction interval of 12 to 90 mg/g, and that a PCR value of 500 mg/g corresponds to an ACR of 220 mg/g (prediction interval 113 to 427 mg/g). These conversions are quite similar to those suggested by KDIGO, in which with dipstick protein values of “trace to +” and “+ or greater” and PCR values of 150-500 mg/g and >500 mg/g should be assigned to albuminuria categories 30-299 mg/g and ≥ 300 mg/g, respectively.[\(12\)](#) In contrast, our results were slightly different at the suggested value of nephrotic range proteinuria, noted as 3000 mg/g PCR or 2220 mg/g ACR in the guideline.[\(12\)](#) Using our crude model, 3000 mg/g PCR corresponded to 1603 mg/g ACR (prediction interval 1015-2532 mg/g).

Despite widespread awareness of the importance of using ACR measurements as the gold standard to assess and monitor CKD, there are still inconsistencies in measurement of ACR versus PCR in clinical practice and in research studies across the world.[\(22\)](#) Since the costs of total protein measurement can be lower than those of albumin measurement, cost considerations may affect implementation of ACR measurement.[\(12\)](#) There may also be clinical reasons for practitioners to use PCR instead of ACR to quantify and monitor clinically significant levels of proteinuria (e.g., in cases of glomerulonephritis or perhaps nephrotic range proteinuria). In this context, our PCR conversion equations may have potential public health, clinical, and research implications from a practical and cost-effective perspective, facilitating the use of PCR as a screening, staging, and prognosis tool for CKD.

Previous studies (based on an English-language MEDLINE search through March 2020) investigating the relationship between PCR and ACR have reported inconsistent results, with some showing strong correlation[\(18-20, 22\)](#) and others not.[\(21\)](#) In a recent study from a population-based cohort of 47,714 adults in Canada,

Weaver et al. derived equations to estimate ACR from PCR, taking into account nonlinearity and modification by several clinical characteristics.(35) At higher levels of PCR, there was an approximately linear relationship between PCR and ACR, but the relationship was less correlated at lower levels, with nearly no relationship at PCR <50 mg/g.(35) Our results were generally consistent with these observations but further increased the generalizability to a large and diverse international population, confirming good concordance of our PCR conversion equations with the current KDIGO estimates.(12) Importantly, these equations could allow for implementation of risk prediction models in which ACR has been incorporated,(13, 15, 16, 36) leading to increased opportunities for practitioners measuring only PCR to utilize these tools for better decision making and patient management. Our results demonstrated similar estimates for KFRE when using predicted (vs. observed) ACR, supporting the potential utility of predicted ACR in risk prediction. Our PCR conversion equations could also facilitate data integration across research studies in a broad range of populations. Although the adjusted equation incorporated sex, hypertension, and diabetes, the coefficient values were small. Given that the crude model is simpler and performs nearly similarly to the adjusted model, the crude equation may be the preferred equation for ease of implementation.

The urine dipstick test has been widely used as an initial screening tool for the evaluation of proteinuria, primarily because of its low cost, simplicity, and ability to provide rapid point-of-care information to both clinicians and patients.(24) However, commonly used reagent strip devices for total protein measurement do not adjust for urinary concentration and provide only semi-quantitative results. Studies have consistently shown low sensitivity of urine dipstick testing for CKD screening (ACR $\geq$ 30 mg/g), despite its high specificity.(23-27) Indeed, in our study, the dipstick trace and greater had low sensitivity (62.0%) but high specificity (87.8%) for detection of ACR $\geq$ 30 mg/g. On the other hand, if detecting CKD stage A3 (ACR $\geq$ 300 mg/g) were the aim, the sensitivity of the “++” category was 77.6%, with a specificity of 97.5%. There are many settings where access to laboratory services is limited and low-cost diagnostic tools such as urine dipstick tests are essential.(24, 25) The performance of these tools should be considered within the local context of test availability, cost, and objectives in considering strategies for CKD screening and staging.

The study results must be interpreted in light of some limitations. We used pairs of PCR and ACR or urine dipstick protein and ACR tested on the same day, but not necessarily in the same urine sample. Thus, we may have overestimated the error in conversion, since albuminuria is subject to intra-individual biological variability, even in the same day, due to a variety of pathological and non-pathological factors (e.g., posture, exercise, fever). Across cohorts, ACR, PCR, and urine dipstick protein were tested in different clinical settings using different laboratory assays, which may also explain some of the observed intra- and inter-cohort variation. Substantial between-laboratory variation has been reported in current assays to measure total urine protein, mostly using either turbidimetry or colorimetry.(17, 37) This is mainly because of a variable mixture of protein in the urine, which makes it difficult to define a standardized reference material for total urine protein measurement.(17) Nevertheless, our results showed a fairly consistent relationship between PCR and ACR across diverse cohorts, at least at levels of PCR 50 mg/g and greater, allowing for the development of ACR equations by combining meta-analyzed beta coefficients with little heterogeneity. For PCR <50 mg/g, we found no consistent association; however, it is fair to say that most corresponding ACR values are <30 mg/g. Finally, caution is warranted in cases of nonalbumin-predominant proteinuria (e.g., α 1-microglobulin, immunoglobulins, and monoclonal heavy or light chains), which may also have diagnostic or prognostic value.(38)

In conclusion, we developed equations for conversion of PCR or urine dipstick protein categories to ACR using random-effects meta-analysis in 33 multinational cohorts. Our PCR conversion equations demonstrated relatively high specificity and sensitivity for the detection of CKD stage A2 and higher, and the 2-year KFRE using predicted ACR performed in a similar manner to that using observed ACR. Although further testing is required to establish the robustness and utility of these equations, our results suggest that, when ACR is not available, predicted ACR may be useful and informative for the purpose of harmonizing across research studies, CKD screening and classification efforts, and use in risk prediction equations.

Supplementary Material

Supplementary Material

[NIHMS1645865-supplement-Supplementary_Material.docx](#) (48.6MB, docx)

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CKD-PC investigators/collaborators (study acronyms/abbreviations are listed in [Appendix 2](#) in the [Supplement](#)

AusDiab: Kevan Polkinghorne, Steven Chadban, Robert Atkins; **CanPREDDICT:** Adeera Levin, Ognjenka Djurdjev, Mila Tang; **CRIC:** Hernan Rincon Choles, Edward Horwitz, Farsad Afshinnia, Raymond R Townsend; **CURE-CKD:** Katherine Tuttle, Kenn B Daratha, Radica Alicic, Cami R Jones; **Geisinger:** Alex R. Chang, Gurmukteshwar Singh, Jamie Green, H. Lester Kirchner; **GLOMMS 2:** Simon Sawhney, Corri Black, Angharad Marks, Lynn Robertson; **ICES-KDT:** Amit Garg; **IDNT:** Hiddo JL Heerspink; **KP Hawaii:** Brian J. Lee; **LCC:** Nigel Brunskill, Rupert Major, David Shepherd, James Medcalf; **MASTERPLAN:** Jack Wetzels, Peter Blankestijn, Arjan van Zuilen, Jan van de Brand; **Moli-Sani:** Massimo Cirillo, Licia Iacoviello; **Mt Sinai BioMe:** Girish N Nadkarni, Erwin P Bottinger, Ruth JF Loos, Stephen B Ellis; **Nefrona:** José M Valdivielso, Marcelino Bermúdez-López, Milica Bozic, Serafí Cambray; **NephroTest:** Benedicte Stengel, Marie Metzger, Martin Flamant, Pascal Houillier, Jean-Philippe Haymann; **NIPPON DATA2010:** Katsuyuki Miura, Akira Okayama, Aya Kadota, Sachiko Tanaka; **OLDW:** Nikita Stempniewicz, John Cuddeback, Elizabeth Ciemins, Emily Carbonara, Stephan Dunning; **Pima:** Robert G. Nelson, William C. Knowler, Helen C. Looker; **PSP-CKD:** Nigel Brunskill, Rupert Major, David Shepherd, James Medcalf; **RCAV:** Csaba P Kovesdy, Keiichi Sumida, Miklos Molnar, Praveen Potukuchi; **RENAAL:** Hiddo JL Heerspink, Michelle Pena, Dick de Zeeuw; **SUN-Macro:** Hiddo JL Heerspink; **Sunnybrook:** David Naimark, Navdeep Tangri; **Takahata:** Takamasa Kayama, Tsuneo Konta; **West of Scotland:** Patrick B Mark, Jamie P Traynor, Peter C Thomson, Colin C Geddes

CKD-PC Steering Committee: Josef Coresh (Chair), Shoshana H Ballew, Alex R. Chang, Ron T Gansevoort, Morgan E. Grams, Orlando Gutierrez, Tsuneo Konta, Anna Köttgen, Andrew S Levey, Kunihiro Matsushita, Kevan Polkinghorne, Elke Schäffner, Mark Woodward, Luxia Zhang

CKD-PC Data Coordinating Center: Shoshana H Ballew (Assistant Project Director), Jingsha Chen (Programmer), Josef Coresh (Principal Investigator), Morgan E Grams (Director of Nephrology Initiatives), Kunihiro Matsushita (Director), Yingying Sang (Lead Programmer), Aditya Surapeneni (Programmer), Mark Woodward (Senior Statistician)

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Footnotes

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Contributor Information

Keiichi Sumida, Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN.

Girish N Nadkarni, Department of Medicine, Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, New York.

Morgan E Grams, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Yingying Sang, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Shoshana H Ballew, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Josef Coresh, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Kunihiro Matsushita, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Aditya Surapaneni, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Nigel Brunskill, John Walls Renal Unit, Leicester General Hospital, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom.

Steve J Chadban, Charles Perkins Centre, University of Sydney, Sydney, Australia.

Alex R Chang, Department of Nephrology and Kidney Health Research Institute, Geisinger Medical Center, Danville, Pennsylvania.

Massimo Cirillo, Department of Public Health, University of Naples “Federico II”, Italy.

Kenn B Daratha, Providence Sacred Heart Medical Center and Gonzaga University School of Anesthesia, Spokane, WA.

Ron T Gansevoort, Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Amit X Garg, ICES, London, Ontario, Canada; Division of Nephrology, Western University, London, Ontario, Canada.

Licia Iacoviello, Department of Epidemiology and Prevention, IRCCS Neuromed, Pozzilli, Italy; Research Center in Epidemiology and Preventive Medicine, Department of Medicine and Surgery, University of Insubria, Varese, Italy.

Takamasa Kayama, Institute for Promotion of Medical Science Research, Yamagata University, Yamagata, Japan.

Tsuneo Konta, Department of Public Health and Hygiene, Yamagata University, Yamagata, Japan.

Csaba P Kovesdy, Medicine-Nephrology, Memphis Veterans Affairs Medical Center and University of Tennessee Health Science Center, Memphis, Tennessee.

James Lash, Division of Nephrology, Department of Medicine, University of Chicago, Chicago, Illinois.

Brian J Lee, Kaiser Permanente, Hawaii Region, Moanalua Medical Center, Honolulu, HI.

Rupert Major, John Walls Renal Unit, Leicester General Hospital, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; Department of Health Sciences, University of Leicester, Leicester, United Kingdom.

Marie Metzger, Clinical Epidemiology Team, Paris Saclay University, Paris-Sud Univ, UVSQ, CESP, INSERM U1018, Villejuif, France.

Katsuyuki Miura, Department of Public Health, Center for Epidemiologic Research in Asia (CERA) Shiga University of Medical Science (SUMS) Seta-Tsukinowa-cho, Shiga, Japan.

David MJ Naimark, Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada.

Robert G Nelson, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona.

Simon Sawhney, University of Aberdeen.

Nikita Stempniewicz, AMGA (American Medical Group Association), Alexandria, Virginia and OptumLabs Visiting Fellow.

Mila Tang, Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada.

Raymond R Townsend, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

Jamie P Traynor, Glasgow Renal Transplant Unit, Queen Elizabeth University Hospital Glasgow Scotland, UK.

Jose M Valdivielso, Vascular & Renal Translational Research Group, IRBLleida, Spain and Spanish Research Network for Renal Diseases (RedInRen. ISCIII), Lleida, Spain.

Jack Wetzels, Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands.

Kevan R. Polkinghorne, Monash University, Clayton, Australia.

Hiddo JL Heerspink, Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center, Groningen, Netherlands.

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Associated Data

This section collects any data citations, data availability statements, or supplementary materials included in this article.

Supplementary Materials

Supplementary Material

[NIHMS1645865-supplement-Supplementary_Material.docx](#) (48.6MB, docx)