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Kunihiro Matsushita
Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.

Simerjot K. Jassal
University of California, San Diego, California

Yingying Sang
Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.

Shoshana H. Ballew
Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.

Morgan E. Grams
Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.

See next page for additional authors

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Research Paper

Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets

Kunihiro Matsushita[a,1], Simerjot K Jassal[b,1], Yingying Sang[a], Shoshana H Ballew[a,*], Morgan E Grams[a], Aditya Surapaneni[a], Johan Arnlov[c], Nisha Bansal[d], Milica Bozic[e], Hermann Brenner[f], Nigel J Brunskill[g,h], Alex R Chang[i], Rajkumar Chinnadurai[j], Massimo Cirillo[k], Adolfo Correa[l], Natalie Ebert[m], Kai-Uwe Eckardt[n,o], Ron T Gansevoort[p], Orlando Gutierrez[q], Farzad Hadaegh[r], Jiang He[s], Shih-Jen Hwang[t], Tazeen H Jafar[u,v,ay], Takamasa Kayama[w], Csaba P Kovesdy[x], Gijs W Landman[y], Andrew S Levey[z], Donald M Lloyd-Jones[aa], Rupert W. Major[g,ab], Katsuyuki Miura[ac], Paul Muntner[ad], Girish N Nadkarni[ae], David MJ Naimark[af], Christoph Nowak[c], Takayoshi Ohkubo[ag], Michelle J Pena[ah], Kevan R Polkinghorne[ai], Charumathi Sabanayagam[aj], Toshimi Sairenchi[ak], Markus P Schneider[n], Varda Shalev[al], Michael Shlipak[am], Marit D Solbu[an], Nikita Stempniewicz[ao], James Tollitt[j,ap], José M Valdivielso[e], Joep van der Leeuw[aq], Angela Yee-Moon Wang[ar], Chi-Pang Wen[as], Mark Woodward[a,at], Kazumasa Yamagishi[au], Hiroshi Yatsuya[av,aw], Luxia Zhang[ax], Elke Schaeffner[m,2], Josef Coresh[a,2]

[a] *Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States*
[b] *Division of General Internal Medicine, University of California, San Diego and VA San Diego Healthcare, San Diego, California*
[c] *Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden*
[d] *Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA, United States*
[e] *Vascular & Renal Translational Research Group, IRBLleida, Spain and Spanish Research Network for Renal Diseases (RedInRen. ISCIII), Lleida, Spain*
[f] *Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ) and Network Aging Research, University of Heidelberg, Heidelberg, Germany*
[g] *John Walls Renal Unit, Leicester General Hospital, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom*
[h] *Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom*
[i] *Department of Nephrology and Kidney Health Research Institute, Geisinger Medical Center, Danville, Pennsylvania*
[j] *Department of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom*
[k] *Department of Public Health, University of Naples "Federico II", Italy*
[l] *University of Mississippi Medical Center, Jackson, United States*
[m] *Institute of Public Health, Charité - Universitätsmedizin Berlin, Berlin, Germany*
[n] *Department of Nephrology and Hypertension, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany*
[o] *Department of Nephrology and Medical Intensive Care, Charité – Universitätsmedizin Berlin, Berlin, Germany*
[p] *Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands*
[q] *Departments of Epidemiology and Medicine, University of Alabama at Birmingham, Birmingham, AL, United States*
[r] *Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[s] *Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, United States*
[t] *National Heart, Lung, and Blood Institute, Framingham, MA, United States*
[u] *Program in Health Services and Systems Research, Duke-National University of Singapore Medical School, Singapore*
[v] *Duke Global Health Institute, Durham, Duke University, NC, United States*
[w] *Global Center of Excellence, Yamagata University Faculty of Medicine, Yamagata, Japan*
[x] *Medicine-Nephrology, Memphis Veterans Affairs Medical Center and University of Tennessee Health Science Center, Memphis, TN, United States*
[y] *Gelre hospital location, Apeldoorn, the Netherlands*
[z] *Division of Nephrology, Tufts Medical Center, Boston, MA, United States*
[aa] *Department of Preventive Medicine, Northwestern University, Chicago, Illinois, United States*
[ab] *Department of Health Sciences, University of Leicester, Leicester, United Kingdom*

For the Chronic Kidney Disease Prognosis Consortium
* Corresponding author.
E-mail addresses: sballew1@jhmi.edu (S.H. Ballew), ckdpc@jhmi.edu (J. Coresh).
[1] Indicates co-first authors.
[2] Indicates co-last authors.

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[ac] Department of Public Health, Center for Epidemiologic Research in Asia (CERA) Shiga University of Medical Science (SUMS) Seta-Tsukinowa-cho, Shiga, Japan
[ad] Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, United States
[ae] Department of Medicine, Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[af] Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada
[ag] Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
[ah] Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands
[ai] Department of Nephrology, Monash Medical Centre, Monashhealth, Melbourne, Australia and Department of Medicine, and Department of Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia
[aj] Singapore Eye Research Institute and Duke-NUS Medical School, Singapore
[ak] Department of Public Health, Dokkyo Medical University School of Medicine, Mibu, Japan
[al] Institute for Health and Research and Innovation, Maccabi Healthcare Services and Tel Aviv University, Tel Aviv, Israel
[am] Department of Epidemiology and Biostatistics, University of California, San Francisco, and San Francisco VA Medical Center, San Francisco, United States
[an] Section of Nephrology, University Hospital of North Norway, Tromsø, Norway and UiT The Arctic University of Norway, Tromsø, Norway
[ao] AMGA (American Medical Group Association), Alexandria, Virginia and OptumLabs Visiting Fellow, United States
[ap] Faculty of Biology, Medicine and Health, University of Manchester, Oxford Road, Manchester, UK
[aq] Department of Vascular Medicine and Department of Nephrology, University Medical Center Utrecht, Utrecht, the Netherlands
[ar] Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong
[as] China Medical University Hospital, Taichung, Taiwan
[at] George Institute for Global Health, Australia, and George Institute for Global Health, Imperial College, London, United Kingdom
[au] Department of Public Health Medicine, Faculty of Medicine, and Health Services Research and Development Center, University of Tsukuba, Japan
[av] Department of Public Health, Fujita Health University School of Medicine, Aichi, Japan
[aw] Department of Public Health and Health Systems, Nagoya University Graduate School of Medicine, Aichi, Japan
[ax] Peking University First Hospital and Peking University, Beijing, China
[ay] Department of Medicine, Aga Khan University, Karachi, Pakistan

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ABSTRACT

Background: Chronic kidney disease (CKD) measures (estimated glomerular filtration rate [eGFR] and albuminuria) are frequently assessed in clinical practice and improve the prediction of incident cardiovascular disease (CVD), yet most major clinical guidelines do not have a standardized approach for incorporating these measures into CVD risk prediction. "CKD Patch" is a validated method to calibrate and improve the predicted risk from established equations according to CKD measures.

Methods: Utilizing data from 4,143,535 adults from 35 datasets, we developed several "CKD Patches" incorporating eGFR and albuminuria, to enhance prediction of risk of atherosclerotic CVD (ASCVD) by the Pooled Cohort Equation (PCE) and CVD mortality by Systematic COronary Risk Evaluation (SCORE). The risk enhancement by CKD Patch was determined by the deviation between individual CKD measures and the values expected from their traditional CVD risk factors and the hazard ratios for eGFR and albuminuria. We then validated this approach among 4,932,824 adults from 37 independent datasets, comparing the original PCE and SCORE equations (recalibrated in each dataset) to those with addition of CKD Patch.

Findings: We confirmed the prediction improvement with the CKD Patch for CVD mortality beyond SCORE and ASCVD beyond PCE in validation datasets (Δc-statistic 0.027 [95% CI 0.018–0.036] and 0.010 [0.007–0.013] and categorical net reclassification improvement 0.080 [0.032–0.127] and 0.056 [0.044–0.067], respectively). The median (IQI) of the ratio of predicted risk for CVD mortality with CKD Patch vs. the original prediction with SCORE was 2.64 (1.89–3.40) in very high-risk CKD (e.g., eGFR 30–44 ml/min/1.73m^2 with albuminuria $\geq$30 mg/g), 1.86 (1.48–2.44) in high-risk CKD (e.g., eGFR 45–59 ml/min/1.73m^2 with albuminuria 30–299 mg/g), and 1.37 (1.14–1.69) in moderate risk CKD (e.g., eGFR 60–89 ml/min/1.73m^2 with albuminuria 30–299 mg/g), indicating considerable risk underestimation in CKD with SCORE. The corresponding estimates for ASCVD with PCE were 1.55 (1.37–1.81), 1.24 (1.10–1.54), and 1.21 (0.98–1.46).

Interpretation: The "CKD Patch" can be used to quantitatively enhance ASCVD and CVD mortality risk prediction equations recommended in major US and European guidelines according to CKD measures, when available.

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1. Introduction

Chronic kidney disease (CKD) affects more than 10% of adults worldwide and increases the risk of many adverse outcomes [1]. Among these, cardiovascular disease (CVD) is particularly important as the leading cause of death in persons with CKD [2]. A number of studies have shown that the key measures of CKD, estimated glomerular filtration rate (eGFR) and albuminuria, are strongly associated with CVD outcomes and can statistically significantly improve the risk prediction of incident CVD beyond traditional CVD risk factors [3,4]. Importantly, eGFR and albuminuria are readily available in many patients.

Despite a body of evidence, major clinical guidelines do not include uniform recommendations for incorporating CKD measures into CVD risk prediction. The American Heart Association (AHA) and the American College of Cardiology (ACC) 2018 Cholesterol Guideline recognizes eGFR <60 ml/min/1.73m^2, but not albuminuria, as a "risk enhancer" but does not specify how to quantitatively enhance the CVD risk estimate. The European Society of Cardiology (ESC) 2016 CVD Prevention Guideline categorizes eGFR <30 ml/min/1.73m^2 in general, or albuminuria in diabetes, as "very high-risk," and eGFR 30–59 ml/min/1.73m^2 as "high-risk;" these designations are equivalent to 10-year risk of CVD mortality of $\geq$10% and 5 to <10%, respectively [5]. This approach does not account for other risk factors and

Research in context

Evidence before this study

We searched PubMed on January 22, 2020 for articles relating to the two key chronic kidney disease (CKD) measures (estimated glomerular filtration rate [eGFR] and albuminuria) using the following terms: ("glomerular filtration rate" or "GFR" or "kidney function") and ("albuminuria" or "proteinuria" or "ACR" or "PCR" or "dipstick") and ("cardiovascular events" or "cardiovascular outcomes" or "cardiovascular mortality" or "myocardial infarction" or "stroke" or "atherosclerotic cardiovascular disease") and ("prediction" or "discrimination" or "calibration" or "c-statistic" or "net reclassification"). Also, we sought feedback on relevant articles form co-authors. Although we found several studies reporting that these CKD measures improved cardiovascular risk prediction, we did not find any studies displaying a specific approach to incorporate CKD measures into established risk prediction models in major clinical guidelines (i.e., the Pooled Cohort Equation [PCE] and SCORE).

Added value of this study

Utilizing data from 4,143,535 adults from 35 datasets, we developed several CKD Patches (tools to enhance predicted risk according to the deviation between an individual's CKD measures and the values expected from their traditional CVD risk factors and the hazard ratios for eGFR and albuminuria) incorporating eGFR and albuminuria, to enhance prediction of risk of atherosclerotic cardiovascular disease (ASCVD) by PCE and CVD mortality by SCORE. In 37 validation datasets including 4,932,824 adults, CKD Patch improved the prediction for CVD mortality beyond SCORE and ASCVD beyond PCE (Δc-statistic 0.027 [95% CI 0.018−0.036] and 0.010 [0.007−0.013] and categorical net reclassification improvement 0.080 [0.032−0.127] and 0.056 [0.044−0.067], respectively). In very high risk CKD (e.g., eGFR 30−44 ml/min/1.73m^2 with urine albumin-to-creatinine ratio $\geq$30 mg/g), the median (IQI) ratio of risk prediction according to the CKD Patch compared to the original equations was 1.55 (1.37−1.81) for ASCVD and 2.64 (1.89−3.40) for CVD mortality.

Implications of all the available evidence

The CKD Patch approach to incorporating eGFR and albuminuria into CVD risk prediction can be used to quantitatively enhance ASCVD and CVD mortality risk prediction equations recommended in major US and European guidelines. Risk prediction incorporating CKD measures is available online for PCE (http://ckdpcrisk.org/ckdpatchpce/) and SCORE (http://ckdpcrisk.org/ckdpatchscore/) and can guide clinical decision making for CVD prevention therapies and physician-patient discussion of CVD predicted risk when these CKD measures are readily available.

therefore may misclassify the risk. Furthermore, this ESC Guideline does not address albuminuria in those without diabetes as a predictor of CVD risk [6].

Importantly, both AHA/ACC and ESC Guidelines have their own risk prediction equations (the Pooled Cohort Equation [PCE] and Systematic COronary Risk Evaluation [SCORE], respectively), which are widely used in primary care settings to guide CVD preventive therapies (e.g., statins). Because CKD measures were not evaluated in the dataset from which PCE and SCORE were derived, these measures cannot be simply incorporated into these risk prediction equations.

To overcome this limitation and enable evidence-based inclusion of eGFR and albuminuria into established CVD risk prediction equations, we meta-analyzed datasets in the CKD Prognosis Consortium (CKD-PC). By applying our previously reported "Predictor Patch" method [7], we developed and validated several "CKD patches" to enhance the predicted CVD risk calculated from PCE and SCORE according to CKD measures. Developing CKD Patches in this meta-analysis which includes ~9 million adults from 72 datasets from various countries has the key advantage of improved generalizability.

2. Methods

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 (#IRB00003324). The need for informed consent was waived by the institutional review board.

2.1. Study populations

We included 72 cohorts in the CKD-PC with available data in the present study. The details of CKD-PC are described elsewhere [8], but in brief, this consortium included both research cohorts and health system datasets, with participants from 41 countries from North America, Europe, the Middle East, Asia, and Australia. These cohorts included general population, high-risk (specifically selected for clinical conditions, such as diabetes), and CKD (exclusively enrolling individuals with CKD) cohorts. We studied participants aged 30 years or older without prevalent CVD at baseline. Each cohort was required to be informative, defined as having at least four years of follow-up among 75% of participants and at least 50 incident CVD outcomes of interest.

2.2. CKD measures

We explored the two key measures of CKD used in nephrology clinical guidelines, and readily available in most clinical settings—eGFR and albuminuria [9]. eGFR was calculated by the CKD Epidemiology Collaboration creatinine equation [10]. Albuminuria was primarily measured as spot urine albumin-to-creatinine ratio (ACR), as recommended in clinical guidelines [9], with secondary analyses utilizing dipstick proteinuria as an alternative measure.

2.3. Traditional CVD predictors

We considered those factors included in either of PCE or SCORE as traditional predictors: age, sex, race, smoking status (current vs. non-current), diabetes, systolic blood pressure, antihypertensive medication use, total cholesterol, and high-density lipoprotein cholesterol [11,12].

2.4. CVD outcomes

CVD outcomes of interest were incident atherosclerotic CVD (ASCVD) and CVD mortality, as evaluated by PCE and SCORE, respectively [11,12]. ASCVD included coronary heart disease (CHD) (myocardial infarction and fatal CHD) and stroke as a composite outcome [11]. Consistent with the SCORE model, we analyzed CHD mortality and non-CHD CVD mortality separately [12]. Details about how each cohort defined ASCVD and CVD mortality are summarized in Web Appendix 1.

2.5. Statistical analysis

All analyses were performed using STATA 14 (College Station, TX) and based on complete data. Cohort characteristics were descriptively compared. As in prior CKD-PC studies [4,13], we analyzed each

cohort separately and then pooled the estimates using random-effects models.

Among the 72 cohorts, 35 cohorts were selected as development datasets because they were able to share de-identified individual-level data with the CKD-PC Data Coordinating Center and represented a broad range of populations, including the general population. The remaining 37 cohorts were either unable to share individual-level data or included highly selected samples (e.g., persons with CKD), and were thus considered validation datasets. One exception was the OptumLabs® Data Warehouse (OLDW) datasets; half were randomly selected to be validation datasets in order to have good representation of health system databases in validation.

We first evaluated the performance of the original PCE and SCORE (both versions of low-risk countries and high-risk countries) in our development datasets. We then developed the "CKD Patch," which contains both eGFR and albuminuria, in the development datasets using a published method [7]. Briefly, there are three steps in the development of the CKD Patch: 1) a linear regression equation was developed to estimate "expected" values of eGFR and log-ACR conditional on the traditional CVD predictors defined above; 2) hazard ratios for the CVD outcomes of interest were estimated for eGFR (with linear spline terms and knots at 60 and 90 ml/min/1.73m^2 [major thresholds of CKD vs. no CKD and reduced vs. normal eGFR, respectively]) [9] and log-ACR, adjusted for the traditional CVD predictors; and 3) the CVD risk estimate was multiplied by the deviation between observed and expected eGFR and log-ACR and their hazard ratios for each individual. In the second step, log hazard ratios for the traditional CVD predictors were fixed according to the original PCE [11] or SCORE [12] coefficients. To match the method used in each original equation, we used Cox models with follow-up time as a time scale for the analysis of ASCVD as in PCE [11] and Weibull models with age as a time scale for the analysis of CVD mortality as in SCORE [12].

The original idea of the "CKD Patch" was to incorporate eGFR and ACR simultaneously [7]. However, to reflect current clinical settings where eGFR is more commonly available than albuminuria, we first developed the GFR Patch. Subsequently, the ACR Patch was added to the GFR Patch, comprising a "CKD Patch." As a sensitivity analysis, we also developed CKD Patch including eGFR and dipstick proteinuria.

The improvement of an established risk equation through the use of additional predictors was predicated on the assumption that the original equation is well calibrated in the cohort of interest (namely, additional predictors generally cannot fix poorly calibrated prediction models). Thus, we evaluated the addition of the various "Patches" after recalibration in each cohort (i.e., calibrating the baseline risk at average levels of predictors and accounting for different average levels among relevant populations) [14]. In CKD cohorts, since expected values from non-CKD cohorts at given levels of traditional predictors were found to overestimate eGFR and underestimate albuminuria, instead of intercept from the linear regression model from the development datasets, we centered expected eGFR and albuminuria at the cohort-specific average.

To evaluate prediction performance in the validation cohorts, we assessed the following: a calibration plot (predicted vs. observed risk) [15], Harrel's c-statistic (a measure of risk discrimination accounting for censoring) [16], and categorical net reclassification improvement (NRI) [17]. The 95% confidence intervals of c-statistics and NRI were calculated using a normal approximation.

2.6. Role of the funding source

The funders had no role in the study design, data collection, analysis, data interpretation, or writing of the report. KM 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.

3. Results

3.1. Study characteristics

The present study included 9,076,359 adults from 72 datasets (4,143,535 adults from 35 development datasets and 4,932,824 adults from 37 validation datasets) (Table 1 and Web Table 1). Mean age within datasets ranged from 44 to 80 years, and most cohorts included 50−60% women. The majority (78%) were White adults, but there were 790,095 (8.7%) Black adults (predominantly from US), 613,727 (6.8%) Asian adults (mainly from Asia), and 319,214 (3.5%) Hispanic adults. Of these 72 datasets, 58 contributed to the analysis of ASCVD and 34 contributed to the analysis of CVD mortality.

Predictor profiles varied considerably across cohorts among the development datasets. For example, the prevalence of antihypertensive medication use ranged from 17% to 77%, which was related to cohort mean age (Pearson correlation 0.76). Datasets from Asia and some from Europe had higher proportions of current smokers than other datasets. Although several validation datasets had a high burden of risk factors by design (e.g., 100% diabetes in a few datasets), the summary characteristics were similar between development datasets and validation datasets.

3.2. Performance of the PCE and score

Baseline survival free of ASCVD across the development datasets is summarized in Web Table 2. Almost all cohorts had higher baseline ASCVD-free survival than the original baseline survival from the PCE, indicating overestimation of ASCVD risk by PCE in these datasets. Indeed, calibration plots confirmed overestimation of ASCVD by PCE in most datasets (Web Fig. 1). Generally, a similar pattern was observed for CVD mortality with SCORE high-risk country calibration (Web Table 3 and Web Fig. 2). On the other hand, SCORE for low-risk countries tended to underestimate CVD mortality in our datasets. For both ASCVD and CVD mortality, baseline survival varied across baseline calendar years (Web Fig. 3).

Once we had recalibrated each equation to each of our datasets, both PCE and SCORE were relatively well calibrated (Web Figs. 1A-C and 2A-C). The pooled c-statistic of PCE was 0.759 (IQI 0.737−0.787) and of SCORE was 0.795 (0.687−0.836), in the development datasets (Web Tables 4 and 5).

3.3. Development of CKD patch

Based on spline models, lower eGFR levels below 60 ml/min/1.73 m^2 were independently associated with increased risk of ASCVD and CVD mortality in the development datasets (Table 2 and Web Fig. 4). However, lower eGFR levels in the range of eGFR ≥90 ml/min/1.73m^2 were associated with decreased risk for both ASCVD and CVD mortality, indicating a known reverse J-shaped association between eGFR and these CVD outcomes likely resulting from an association between frailty and low muscle mass [3]. Higher ACR was linearly associated with both ASCVD and CVD mortality. Elevated dipstick proteinuria categories were associated with higher ASCVD risk, but were less consistent for CVD mortality. Overall, as reported previously [3], both eGFR and ACR demonstrated stronger associations with CVD mortality than with ASCVD.

In the linear regression models to estimate "expected" levels of CKD measures, age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, the use of antihypertensive medication, current smoking, diabetes, and black race were all statistically significantly associated with eGFR levels (Web Table 6). ACR was also associated with all of these factors except black race. Gender was associated with ACR but not eGFR. The models for estimating "expected" eGFR and log-ACR were similar in datasets used for developing the "CKD Patch" for ASCVD and CVD mortality (Web Table 6).

Table 1
Baseline characteristics for development and validation datasets.

Study	N	Age (SD), y	Female,%	eGFR (SD), ml/min/1.73m^2	N, ACR	ACR (IDI), mg/g*	N, Urine Dipstick	Dipstick ≥1+, %
Development datasets								
Aichi	4701	49 (7)	21	100 (13)			4543 (97%)	2.25
ARIC	10,056	63 (6)	59	87 (16)	9969 (99%)	4 (2–7)		
AusDiab	8234	52 (13)	56	86 (15)	8229 (100%)	5 (4–8)		
BIS	1625	80 (7)	54	65 (17)	1622 (100%)	10 (5–30)	1611 (99%)	15.99
China NS	33,448	50 (12)	59	99 (16)	33,448 (100%)	7 (3–15)	32,946 (98%)	4.58
CIRCS	4083	53 (9)	47	93 (14)			4083 (100%)	3.23
COBRA	1008	53 (11)	63	98 (20)	1006 (100%)	6 (4–15)		
ESTHER	4908	62 (7)	57	84 (20)			4806 (98%)	10.24
Framingham	2837	59 (10)	55	89 (19)	2837 (100%)	6 (3–15)		
Geisinger	313,550	53 (14)	55	88 (20)	67,068 (21%)	9 (4–25)		
Gubbio	4246	53 (14)	56	85 (15)	1620 (38%)	9 (4–14)		
Maccabi	1088,168	49 (14)	55	98 (18)	280,759 (26%)	15 (9–32)		
MESA	6757	62 (10)	53	83 (17)	6747 (100%)	5 (3–11)		
Mt Sinai BioMe	14,380	54 (13)	61	82 (24)	4903 (34%)	11 (4–51)		
NHANESIII	10,889	53 (16)	54	95 (22)	10,666 (98%)	6 (4–13)		
NHANEScon	27,277	53 (15)	52	90 (22)	27,047 (99%)	7 (4–13)		
Ohasama	1486	63 (9)	66	96 (13)			1479 (100%)	7.30
OLDW cohort 1	210,841	54 (14)	59	86 (19)	35,008 (17%)	11 (6–30)	63,701 (30%)	8.94
OLDW cohort 2	171,715	57 (14)	55	84 (19)	26,458 (15%)	12 (6–30)	48,289 (28%)	10.20
OLDW cohort 3	153,271	54 (14)	58	89 (18)	28,061 (18%)	8 (4–19)	103,707 (68%)	9.30
OLDW cohort 4	466,471	55 (14)	55	86 (20)	88,129 (19%)	12 (7–30)	162,156 (35%)	9.41
OLDW cohort 5	33,817	55 (14)	59	84 (20)	3786 (11%)	9 (4–27)	13,676 (40%)	5.09
OLDW cohort 6	86,466	50 (11)	60	95 (21)	27,277 (32%)	12 (6–37)	20,556 (24%)	11.98
OLDW cohort 7	95,085	57 (15)	58	82 (21)	14,124 (15%)	9 (5–23)	58,470 (61%)	7.07
OLDW cohort 8	113,743	53 (13)	59	90 (20)	16,208 (14%)	12 (6–34)	24,658 (22%)	6.08
OLDW cohort 9	206,645	56 (14)	56	86 (20)	40,149 (19%)	9 (5–25)	68,465 (33%)	9.26
OLDW cohort 10	101,483	56 (14)	58	85 (20)	17,601 (17%)	9 (5–25)	26,954 (27%)	6.10
OLDW cohort 11	36,724	53 (13)	60	88 (20)	5631 (15%)	12 (6–28)	11,573 (32%)	7.97
OLDW cohort 12	125,067	53 (13)	55	87 (20)	18,885 (15%)	11 (6–29)	31,132 (25%)	10.66
OLDW cohort 13	782,375	54 (13)	57	87 (20)	107,390 (14%)	9 (5–26)	251,414 (32%)	10.72
PREVEND	6105	50 (12)	55	96 (16)	6101 (100%)	7 (5–13)		
Rancho Bernardo	1305	70 (12)	62	66 (16)	1301 (100%)	6 (3–13)		
Takahata	3262	62 (10)	56	99 (12)	3246 (100%)	9 (6–18)	3257 (100%)	4.48
Tromso	10,525	60 (8)	58	92 (12)	10,277 (98%)	4 (3–7)	10,252 (97%)	0.86
ULSAM	982	71 (1)	0	76 (11)	975 (99%)	8 (5–17)		
Total	4143,535	53 (14)	56	90 (20)	906,528 (22%)	15 (9–32)	947,728 (23%)	9.28
Validation datasets								
ADVANCE	8412	66 (6)	46	78 (17)	8070 (96%)	15 (7–38)		
CARDIA	4409	37 (5)	55	108 (23)	4364 (99%)	4 (3–7)		
CHS	2399	78 (5)	64	67 (16)	2105 (88%)	9 (5–20)		
CRIC	2757	57 (11)	47	46 (16)	2631 (95%)	42 (8–419)		
GCKD	3687	60 (11)	44	50 (18)	3670 (100%)	54 (10–425)		
Hong Kong CKD	326	60 (12)	46	18 (7)				
IPHS	92,345	59 (10)	66	86 (14)			92,060 (100%)	2.32
JHS	2652	50 (11)	63	99 (20)	1831 (69%)	6 (4–10)		
LCC	10,248	76 (10)	65	52 (13)	4792 (47%)	9 (4–31)		
NEFRONA	1259	60 (11)	40	33 (17)	864 (69%)	91 (12–409)		
NIPPON DATA80	8826	50 (13)	56	88 (17)			8815 (100%)	2.64
NIPPON DATA90	7497	52 (14)	59	98 (16)			7396 (99%)	2.50
OLDW cohort 14	84,265	56 (13)	59	82 (19)	11,334 (13%)	14 (7–34)	20,286 (24%)	10.27
OLDW cohort 15	90,051	56 (14)	60	87 (21)	15,170 (17%)	10 (5–28)	39,295 (44%)	10.00
OLDW cohort 16	468,725	53 (13)	58	90 (21)	49,449 (11%)	13 (6–30)	186,746 (40%)	8.52
OLDW cohort 17	24,549	56 (13)	59	84 (20)	3271 (13%)	13 (7–36)	10,388 (42%)	11.09
OLDW cohort 18	95,738	53 (13)	59	88 (18)	15,948 (17%)	8 (4–22)	29,246 (31%)	10.61
OLDW cohort 19	360,879	54 (13)	55	86 (19)	53,235 (15%)	10 (5–27)	93,155 (26%)	9.65
OLDW cohort 20	94,596	55 (13)	52	83 (19)	12,709 (13%)	12 (6–32)	30,997 (33%)	8.86
OLDW cohort 21	204,861	55 (14)	57	85 (19)	23,498 (11%)	11 (6–28)	72,462 (35%)	10.25
OLDW cohort 22	136,301	54 (14)	51	86 (19)	20,044 (15%)	10 (5–29)	44,190 (32%)	5.75
OLDW cohort 23	90,989	54 (13)	56	88 (19)	11,269 (12%)	13 (7–32)	18,561 (20%)	8.32
OLDW cohort 24	95,652	52 (12)	56	88 (18)	11,002 (12%)	8 (4–23)	34,707 (36%)	11.65
OLDW cohort 25	749,323	55 (14)	57	85 (19)	92,450 (12%)	13 (6–37)	195,854 (26%)	9.09
OLDW cohort 26	84,918	54 (14)	58	89 (22)	17,014 (20%)	9 (4–28)	25,666 (30%)	10.32
OLDW cohort 27	32,485	51 (14)	55	90 (18)	5038 (16%)	8 (4–20)	6839 (21%)	10.51
RCAV	1425,737	61 (13)	7.3	82 (17)	386,160 (27%)	9 (4–29)		
REGARDS	21,773	65 (9)	58	86 (19)	1146 (100%)	7 (4–14)		
RENAAL	1146	60 (8)	39	41 (13)	21,270 (98%)	1283 (568–2631)		
SEED	8390	58 (10)	52	85 (19)	6050 (72%)	13 (7–27)		
SKS	1585	64 (14)	40	34 (17)				
SMART	5427	54 (12)	45	87 (19)	2975 (55%)	10 (5–25)		
Sunnybrook	1727	64 (16)	43	52 (28)	1149 (67%)	80 (17–346)	722 (42%)	
TaiwanMJ	319,400	45 (12)	50	91 (16)			315,680 (99%)	6.94
TLGS	10,148	44 (12)	56	80 (15)			5797 (57%)	2.73

(*continued*)

Table 1 (*Continued*)

Study	N	Age (SD), y	Female,%	eGFR (SD), ml/min/1.73m^2	N, ACR	ACR (IDI), mg/g*	N, Urine Dipstick	Dipstick ≥1+, %
UK Biobank	378,133	57 (8)	55	91 (13)	367,315 (97%)	6 (4–10)		
ZODIAC	1209	67 (12)	60	68 (17)	1183 (98%)	2 (1–6)		
Total	4932,824	56 (14)	42	86 (19)	1,157,006 (23%)	9 (4–29)	1,238,862 (25%)	7.92

* N for ACR or dipstick are a subset of the cohorts. ACR: urine albumin to creatinine ratio; eGFR: estimated glomerular filtration rate.

Table 2
Meta-analyzed hazard ratios (95% CI) in development datasets.

Variables	ASCVD	Fatal CHD	non-CHD CVD mortality
eGFR patch			
eGFR <60, −15 ml	**1.30 (1.26, 1.35)**	**1.72 (1.46, 2.04)**	**1.61 (1.31, 1.98)**
eGFR 60–90, −15 ml	**0.91 (0.88, 0.94)**	1.08 (0.96, 1.22)	**1.09 (1.01, 1.17)**
eGFR 90+, −15 ml	**0.71 (0.66, 0.75)**	**0.75 (0.67, 0.83)**	**0.80 (0.66, 0.95)**
ACR patch on top of eGFR patch			
ACR, 8 fold	**1.34 (1.28, 1.41)**	**1.60 (1.47, 1.74)**	**1.67 (1.51, 1.86)**
Dipstick patch on top of eGFR patch			
Dipstick trace	**1.28 (1.22, 1.34)**	0.80 (0.55, 1.18)	1.33 (0.87, 2.01)
Dipstick +	**1.50 (1.38, 1.63)**	**2.16 (1.17, 3.98)**	**1.51 (1.13, 2.03)**
Dipstick ++	**1.93 (1.74, 2.13)**	1.91 (0.99, 3.67)	**3.26 (1.98, 5.39)**
Dipstick +++	**2.18 (1.98, 2.41)**	**4.03 (1.44, 11.29)**	5.07 (0.71, 36.02)

ACR: urine albumin to creatinine ratio; ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate.
Bold indicates statistical significance at p<0.05.

Table 3
C-statistics and NRI for ASCVD and CVM in validation datasets.

		ASCVD		CVM	
		eGFR patch	CKD patch	eGFR patch	CKD patch
N		4,489,273	1,153,790	875,693	419,732
Base C-statistic (IQI)		0.755 (0.698, 0.772)	0.687 (0.665, 0.726)	0.711 (0.621, 0.790)	0.680 (0.569, 0.732)
ΔC-statistic (95% CI)		0.002 (0.001, 0.002)	0.010 (0.007, 0.013)	0.008 (0.005, 0.011)	0.027 (0.018, 0.036)
Categorical NRI (95% CI) cut point at 7.5%, 20% for ASCVD, 5% and 10% for CVM	Overall	0.039 (0.031, 0.047)	0.056 (0.044, 0.067)	0.035 (0.013, 0.056)	0.080 (0.032, 0.127)
	Event	0.059 (0.050, 0.068)	0.084 (0.066, 0.102)	0.070 (0.046, 0.094)	0.065 (0.007, 0.123)
	Non-event	−0.020 (−0.023, −0.017)	−0.016 (−0.027, −0.005)	−0.028 (−0.033, −0.023)	0.037 (−0.007, 0.080)

ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; CVM: cardiovascular mortality; eGFR: estimated glomerular filtration rate; NRI: net reclassification improvement.

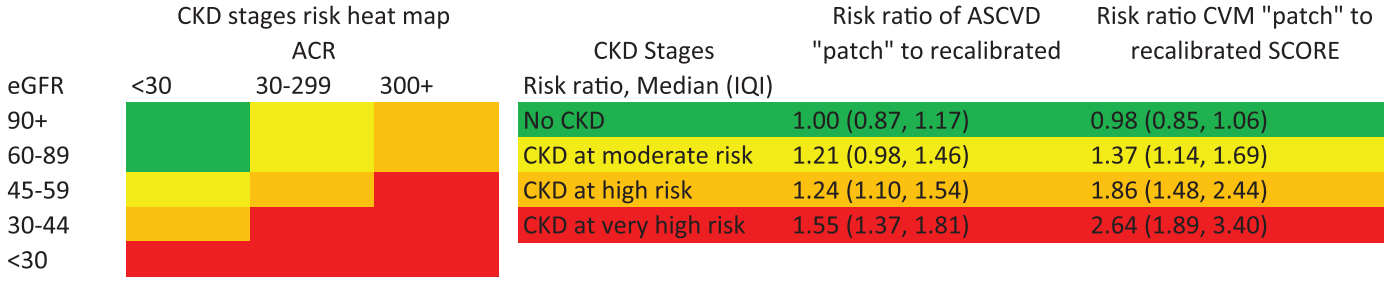

Fig. 1. Enhancement of ASCVD and CVM risk by CKD status. ACR: urine albumin to creatinine ratio; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; CVM: cardiovascular disease mortality; eGFR: estimated glomerular filtration rate. eGFR in ml/min/1.73m^2 and ACR in mg/g.

Using these estimates, we constructed the "CKD Patch" for ASCVD and CVD mortality separately.

3.4. Performance of CKD patch in validation datasets

Among 29 validation datasets (n = 4489,273) with ASCVD data, the GFR Patch did not alter model calibration (Web Fig. 1B-C) but slightly improved the c-statistic by 0.002 (95% CI 0.001–0.002) compared to recalibrated PCE (Table 3 and Web Table 7). The improvement was more evident with the CKD Patch (including eGFR and ACR) (Δc-statistic 0.010 [0.007–0.013]). Of 29 datasets, only four showed a lower c-statistic with CKD Patch, but none of these reached statistical significance. On the other hand, 16 datasets showed a statistically significant improvement of risk discrimination. NRI was statistically significantly positive (indicating improved reclassification) for both the GFR Patch (0.039 [0.031, 0.047]) and the CKD Patch (0.056 [0.044, 0.067]) (Web Table 8).

The improvement in risk prediction with the GFR Patch and the CKD Patch (with eGFR and ACR) was also observed in the 17 validation datasets (n = 875,693) for CVD mortality data (Table 3 and Web Table 7). Δc-statistic was 0.008 (0.005–0.011) for the GFR Patch and 0.027 (0.018–0.036) for the CKD Patch. NRI was 0.035 (0.013–0.056) for GFR Patch and 0.080 (0.032–0.127) for CKD Patch. (Web Table 8).

The CKD Patch with eGFR and dipstick proteinuria also improved prediction of ASCVD and CVD mortality in the validation datasets (Web Tables 9 and 10). Improvements in validation cohorts were similar to those in the development cohorts (Web Tables 11 and 12).

3.5. Absolute risk estimates using the CKD patch with the PCE or score equations

We compared predicted risk with and without the CKD Patch (available at http://ckdpcrisk.org/ckdpatchpce/ and http://ckdpcrisk.org/ckdpatchscore/) (equations in Web Table 13) for recalibrated risk estimates by PCE for ASCVD and by SCORE for CVD mortality in the validation datasets (Fig. 1). The CKD Patch enhanced the predicted CVD risk in participants with lower eGFR and higher albuminuria. For example, across cohorts, the median ratio (IQI) of the ASCVD risk by PCE with the CKD Patch to ASCVD risk by PCE without the CKD Patch was 1.55 (1.37−1.81) in CKD at very high risk (e.g., eGFR 30−44 ml/min/1.73 m^2 with albuminuria ≥30 mg/g), 1.24 (1.10−1.54) in CKD at high risk (e.g., eGFR 45−59 ml/min/1.73 m^2 with albuminuria 30−299 mg/g), and 1.21 (0.98−1.46) in CKD at moderate risk (e.g., eGFR 60−89 ml/min/1.73 m^2 with albuminuria 30−299 mg/g) (Fig. 1) [9], indicating considerable ASCVD risk underestimation in CKD by PCE. The corresponding ratios were even greater for CVD mortality by SCORE, with a median of 2.64 (1.89−3.40) for very high, 1.86 (1.48−2.44) for high, and 1.37 (1.14−1.69) for moderate risk CKD. The percentage of individuals with eGFR <30 ml/min/1.73 m^2 classified at very high risk for CVD mortality (>10% in 10 years) increased from 30.9% to 53.5% by adding the eGFR patch to the recalibrated SCORE, compared to 14.2% and 29.0% for the original SCORE for low- and high-risk countries (Web Table 14).

4. Discussion

There are several key findings from this study. First, after recalibration, PCE and SCORE showed good discrimination across the cohorts in our global Consortium. Second, the "CKD Patch" improved discrimination and CVD risk classification beyond recalibrated PCE for ASCVD and recalibrated SCORE for CVD mortality. Third, the improvement by the CKD Patch was generally more evident for CVD mortality prediction than for ASCVD prediction. Fourth, as expected and now quantified, the impact on CVD risk was larger at lower eGFR and higher ACR (defined by KDIGO as higher risk CKD categories). Finally, the calibration of the original PCE and SCORE equations varied markedly across a broad range of international datasets.

Whether the changes in c-statistic with addition of the CKD Patch in our study (e.g., 0.010 for ASCVD and 0.027 for CVD mortality) are clinically meaningful deserves some discussion. These values may look small but are actually a magnitude ∼5−10 times larger than what was reported for the addition of high-sensitivity C-reactive protein or fibrinogen for ASCVD in an international meta-analysis [18]. Importantly, unlike most non-traditional predictors, eGFR is routinely assessed in clinical practice (e.g., hundreds of millions of tests of serum creatinine are conducted annually in the USA), and the assessment of albuminuria is a non-invasive test recommended for individuals with diabetes, hypertension, and CKD by major clinical guidelines. Thus, instead of a typical question of whether it is worth additionally measuring non-traditional predictors, the question for CKD measures is whether healthcare providers should ignore readily available information on CKD measures in CVD risk prediction. Our results clearly indicate that the answer is no.

The fundamental concept of a "CKD Patch" is consistent with the new concept of "risk enhancers" in the AHA/ACC 2018 Cholesterol Guideline. However, the AHA/ACC Guideline does not specify how to quantitatively enhance predicted risk based on kidney dysfunction. Our approach of the "CKD Patch" provides an objective method for enhancing predicted ASCVD risk by incorporating quantitative values of both CKD measures into PCE (http://ckdpcrisk.org/ckdpatchpce/). As shown in Fig. 1, not incorporating CKD measures leads to underestimation of ASCVD risk in a majority of individuals with very high-risk CKD (e.g., eGFR 30−44 ml/min/1.73m^2 with ACR 30−299 mg/g) and high-risk CKD (e.g., eGFR 45−59 ml/min/1.73m^2 with ACR 30−299 mg/g) by ∼55% and ∼25%, respectively.

The "CKD Patch" improved risk prediction of CVD mortality more than that of ASCVD. This is consistent with our previous report which demonstrated that CKD measures were more strongly associated with CVD mortality and heart failure compared to ASCVD [3]. These observations have biological plausibility since left ventricular hypertrophy [19] and accompanying diastolic dysfunction have been recognized as the most common cardiac phenotype related to CKD [2], and these conditions can lead to development of heart failure, a condition with high mortality.

This risk enhancement, quantified by the CKD Patch (http://ckdpcrisk.org/ckdpatchscore/), in the prediction of CVD mortality has important implications for the ESC CVD Prevention Guideline, which has focused on risk of CVD mortality to guide preventive approaches. The ESC Guideline provides general estimates of CVD mortality risk by CKD status while our CKD Patch refines CVD mortality risk prediction by adding CKD measures to traditional risk factors. For example, our risk tool predicts CVD mortality in persons with CKD at very high risk (red categories in Fig. 1) as ∼2.5 times higher than that predicted by SCORE with appropriate calibration. Therefore, some individuals with eGFR 30−59 ml/min/1.73m^2 will have very high risk, likely requiring preventive medications, while the current European guideline classified all as having high risk (10-y CVD mortality risk of 5−9%) and emphasized intensive lifestyle advice.

We demonstrated heterogeneity across datasets in baseline survival free of CVD beyond what is explained by the traditional predictors, indicating that one size would not fit all [20]. This observation is not surprising since the incidence rate of CVD varies substantially by factors beyond traditional predictors, such as socioeconomic status, lifestyle, region/country, and calendar year. Different methods have been proposed to optimize calibration, e.g., recalibrating an existing equation [14] or developing a unique equation to specific regions/countries [21] or clinical groups (e.g., diabetes) [22]. Alternatively, a few groups have proposed a method to utilize national data to tailor risk prediction for each country [20,23]. A limitation of all approaches is that incidence rates often change over time due to various reasons (e.g., the development of novel therapies).

There are several limitations of this study. The assessment of CKD measures and traditional risk factors was not fully standardized across cohorts. Similarly, the ascertainment and definitions of CVD were not identical across cohorts. We relied on an assessment of eGFR and albuminuria at a single timepoint. Also, we did not have information on primary causes of CKD. In addition, the validation datasets were not necessarily randomly selected. However, our validation datasets with varying study characteristics seem actually conservative and advantageous in terms of generalizability. Although our cohorts represent 41 countries, we have only a few cohorts that include participants from South America, the Middle East, and Australia, and no cohorts from Africa. The complete case data analysis can be also viewed as a limitation. However, the results were largely consistent in research cohorts and clinical database studies; mechanisms of missing data can be considerably different in these two study types (typically sicker populations tend to have missing data in research cohorts, whereas clinical databases will oversample sicker populations who are more likely to have more laboratory measurements).

In conclusion, eGFR and albuminuria enhance CVD risk prediction. The "CKD Patch" developed in this study enables objective calibration of CVD risk in CKD at higher risk, defined by lower eGFR and higher albuminuria, and improvement of two major existing prediction models, the PCE for ASCVD and SCORE for CVD mortality.

Data sharing statement

Under agreement with the participating cohorts, CKD-PC cannot share individual data with third parties. Inquiries regarding specific analyses should be made to ckdpc@jhmi.edu. Investigators may approach the original cohorts regarding their own policies for data sharing (e.g., https://sites.cscc.unc.edu/aric/distribution-agreements for the Atherosclerosis Risk in Communities Study).

Contributors

K.M. and J.C. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. K.M. and J.C. were responsible for the study concept and design. K.M., Y.S., S.H.B., M.E.G., A.S., and J.C with the CKD-PC investigators/collaborators listed below were involved in the acquisition of data. All the authors contributed to the analysis and interpretation of data and to the critical revision of the manuscript for important intellectual content. K.M., S.K.J., Y.S., S.H.B., E.S., and J.C. drafted the manuscript. K.M. and J.C. guarantee the integrity of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CKD-PC investigators/collaborators (cohort acronyms/abbreviations are listed in eAppendix 2 in the Supplement:

ADVANCE: John Chalmers, Mark Woodward; Aichi: Hiroshi Yatsuya, Koji Tamakoshi, Yuanying Li, Yoshihisa Hirakawa; ARIC: Josef Coresh, Kunihiro Matsushita, Jung-Im Shin, Junichi Ishigami; AusDiab: Kevan Polkinghorne, Steven Chadban, Robert Atkins; BIS: Elke Schaeffner, Natalie Ebert, Dörte Huscher; CARDIA: Donald Lloyd-Jones, Orlando M. Gutierrez; China NS: Luxia Zhang, Minghui Zhao, Fang Wang, Bixia Gao, Jinwei Wang; CHS: Michael Shlipak, Nisha Bansal; CIRCS: Hiroyasu Iso, Kazumasa Yamagishi, Isao Muraki, Yasuhiko Kubota; COBRA: Tazeen Jafar, Imtiaz Jehan, Neil Poulter, Nish Chaturvedi; CRIC: Jiang He, Wei Yang, Matthew Weir, Stephanie Toth-Manikowski, Christopher Jepson; ESTHER: Hermann Brenner, Dietrich Rothenbacher, Ben Schöttker, Bernd Holleczek; Framingham: Daniel Levy, Shih-Jen Hwang; GCKD: Markus P. Schneider, Anna Köttgen, Heike Meiselbach, Kai-Uwe Eckardt; Geisinger: Alex R. Chang, Gurmukteshwar Singh, Jamie Green, H. Lester Kirchner; Gubbio: Massimo Cirillo; Hong Kong CKD: Angela Yee-Moon Wang, Hoi Ching Cheung, Hailey Yee Tsui, Victoria Ngai; IPHS: Fujiko Irie, Toshimi Sairenchi; JHS: Adolfo Correa, Casey M. Rebholz, Bessie Young, L. Ebony Boulware; LCC: Nigel Brunskill, Laura Gray, Rupert W. Major, James Medcalf; Maccabi: Varda Shalev, Gabriel Chodick; MESA: Michael Shlipak; Mt Sinai BioMe: Girish N. Nadkarni, Erwin P. Bottinger, Ruth J.F. Loos, Stephen B. Ellis; NEFRONA: José M. Valdivielso, Marcelino Bermúdez-López, Milica Bozic, Serafí Cambray; NHANES: Yingying Sang; NIPPON DATA80 & NIPPON DATA90: Hirotsugu Ueshima, Akira Okayama, Tomonori Okamura, Katsuyuki Miura; Ohasama: Takayoshi Ohkubo, Hirohito Metoki, Michihiro Satoh, Masahiro Kikuya; OLDW: John Cuddeback, Elizabeth Ciemins, Emily Carbonara, Stephan Dunning; PREVEND: Ron T. Gansevoort, Lyane M. Kieneker, Stephan J.L. Bakker, Hans L. Hillege, Pim van der Harst; Rancho Bernardo: Simerjot K. Jassal, Jacklyn Bergstrom, Joachim Ix; RCAV: Csaba P. Kovesdy, Keiichi Sumida, Miklos Z. Molnar, Praveen Potukuchi; REGARDS: Orlando M. Gutierrez, Paul Muntner, David Warnock; RENAAL: Dick de Zeeuw, Michelle J. Pena, Hiddo J.L. Heerspink; SEED: Tien Yin Wong, Charumathi Sabanayagam, Ching-Yu Cheng, Rehena

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CKD-PC Steering Committee: Josef Coresh (Chair), Shoshana H. Ballew, Alex R. Chang, Ron T. Gansevoort, Morgan E. Grams, Orlando M. 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).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100552.

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