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FULL RESEARCH PAPER
Risk prediction/assessment & stratification

Including measures of chronic kidney disease to improve cardiovascular risk prediction by SCORE2 and SCORE2-OP

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Aims The 2021 European Society of Cardiology (ESC) guideline on cardiovascular disease (CVD) prevention categorizes moderate and severe chronic kidney disease (CKD) as high and very-high CVD risk status regardless of other factors like age and does not include estimated glomerular filtration rate (eGFR) and albuminuria in its algorithms, systemic coronary risk estimation 2 (SCORE2) and systemic coronary risk estimation 2 in older persons (SCORE2-OP), to predict CVD risk. We developed and validated an 'Add-on' to incorporate CKD measures into these algorithms, using a validated approach.

Methods In 3,054 840 participants from 34 datasets, we developed three Add-ons [eGFR only, eGFR + urinary albumin-to-creatinine ratio (ACR) (the primary Add-on), and eGFR + dipstick proteinuria] for SCORE2 and SCORE2-OP. We validated C-statistics and net reclassification improvement (NRI), accounting for competing risk of non-CVD death, in 5,997 719 participants from 34 different datasets.

Results In the target population of SCORE2 and SCORE2-OP without diabetes, the CKD Add-on (eGFR only) and CKD Add-on (eGFR + ACR) improved C-statistic by 0.006 (95%CI 0.004–0.008) and 0.016 (0.010–0.023), respectively, for SCORE2 and 0.012 (0.009–0.015) and 0.024 (0.014–0.035), respectively, for SCORE2-OP. Similar results were seen when we included individuals with diabetes and tested the CKD Add-on (eGFR + dipstick). In 57 485 European participants with CKD, SCORE2 or SCORE2-OP with a CKD Add-on showed a significant NRI [e.g. 0.100 (0.062–0.138) for SCORE2] compared to the qualitative approach in the ESC guideline.

Conclusion Our Add-ons with CKD measures improved CVD risk prediction beyond SCORE2 and SCORE2-OP. This approach will help clinicians and patients with CKD refine risk prediction and further personalize preventive therapies for CVD.

Keywords Chronic kidney disease • Cardiovascular disease • Risk prediction • Meta-analysis

Introduction

Chronic kidney disease (CKD) affects more than 10% of the adult population globally and is widely recognized as an important risk factor for cardiovascular disease (CVD).[1,2] Indeed, in the 2021 European Society of Cardiology (ESC) guideline on CVD prevention,[3] individuals with moderate and severe CKD [according to the Kidney Disease: Improving Global Outcomes staging system based on reduced glomerular filtration rate (GFR) and elevated albuminuria[4]] are regarded as high and very high-risk of CVD, respectively. However, such a qualitative approach misses an opportunity to personalize CVD preventive therapies according to quantitative measures of CKD, which are often readily available in clinical practice, in addition to traditional CVD risk factors.

We recently developed and validated a new approach, 'CKD Add-on',[5] that allows the inclusion of information on the two CKD measures, GFR and albuminuria, into existing prediction models. With this approach, the original predicted risk of CVD is calibrated in the individual participant having GFR (or albuminuria) that differs from their expected GFR based upon the profile of their demographic and risk factor characteristics. Using this approach, the two CKD measures have significantly improved CVD risk prediction beyond two reference CVD risk prediction models, the Pooled Cohort Equation (PCE)[6] and SCORE.[5, 7]

Here, we sought to develop and validate a CKD Add-on for systemic coronary risk estimation 2 (SCORE2) and SCORE2 in older persons (SCORE2-OP) (i.e. the risk prediction algorithms adopted by the 2021 ESC CVD prevention guideline), using data from the CKD Prognosis Consortium (CKD-PC). We also compared risk classification between our quantitative approach with a CKD Add-on and the qualitative approach proposed in the 2021 ESC guideline.

Methods

Study populations

The data sources were 68 datasets taking part in CKD-PC with individual-level data necessary for this specific study (namely, GFR, albuminuria, traditional CVD risk factors, and CVD outcomes defined below). These cohorts included both prospective research cohorts and health system datasets and enrolled participants from 41 countries from Europe, the Middle East, Asia, Australasia, and the Americas. These cohorts represented general population cohorts (no specific selection of some clinical conditions), high-risk cohorts (selection of some specific clinical conditions but not exclusively CKD), and CKD cohorts (explicit inclusion of individuals with CKD). This project included cohorts with 50 or more CVD outcomes and 95th percentile of follow-up time longer than 5 years among eligible participants without a history

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of CVD at baseline. 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, MD, USA (no. IRB00003324). The need for informed consent was waived by the institutional review board.

Both SCORE2 and SCORE2-OP were designed for adults aged 40–69 years and those aged ≥70 years, respectively, but were derived from datasets including individuals with broader age ranges. Such an age margin is advantageous to obtain reliable coefficients of the interaction terms between age and predictors at relevant age thresholds. Thus, for the development of the CKD Add-on, we applied an age margin of 10 years and included all eligible adults aged ≥30 years for SCORE2 and those aged ≥60 years for SCORE2-OP.[8] Nonetheless, as detailed below, the validation of the CKD Add-on was restricted to individuals in the target age range of SCORE2 (40–69 years) and SCORE2-OP (≥70 years).

The 2021 ESC guideline classifies all individuals with diabetes mellitus as moderate to very high risk according to the disease duration and the presence of end organ damage.[3] SCORE2 algorithms are therefore proposed for individuals without diabetes.[8] However, the development of SCORE2 algorithms included diabetes as a covariate, to facilitate recalibration of the models using CVD incidence rates from the general population that included individuals with diabetes.[8] Thus, we also included individuals with diabetes in the development of the CKD Add-on. Nonetheless, to match the proposed target population of SCORE2 algorithms, our primary validation was focused on the population without diabetes, and we secondarily explored data from the entire population including diabetes.

CKD measures

We focused on the two key CKD measures used for CKD staging in nephrology clinical guidelines, GFR, and albuminuria.[4] Estimated GFR (eGFR) was calculated using the 2021 CKD Epidemiology Collaboration (CKD-EPI) creatinine-based equation (but results were similar when an Add-on was developed for the 2009 CKD-EPI eGFR creatinine-based equation).[9] Albuminuria was ascertained primarily as urine albumin-to-creatinine ratio (ACR)[4] but secondarily included dipstick proteinuria. Data on urine protein-to-creatinine ratio were converted to ACR using a validated equation when ACR information was not available.[10]

Traditional CVD risk factors

We considered the following predictors in SCORE2 and SCORE2-OP as traditional CVD risk factors: age, sex, smoking status (current vs. non-current), diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol.

CVD outcome

Following the development process of SCORE2 and SCORE2-OP,[8] CVD outcome of interest was a composite of myocardial infarction, stroke, and CVD mortality. Supplementary material online, *Appendix S1* summarizes details of how each cohort defined CVD events.

Statistical analysis

We first summarized characteristics [e.g. continuous variables as mean (SD) or median (IQI) and categorical variables as proportion or counts] in development and validation datasets. In general, we conducted two-stage meta-analysis in which each cohort was analyzed separately, and then the relevant estimates were pooled using random-effects models.[11,12]

Following the process of developing the CKD Add-ons for PCE and SCORE,[5] we used 34 datasets able to share de-identified individual-level data with the CKD-PC Data Coordinating Centre as development datasets. These datasets represented a wide range of populations, including the general population. The remaining 33 datasets, which could not share individual-level data or included highly selected populations (e.g. only CKD patients), were included as validation datasets. An exception was that we randomly split the OptumLabs® Data Warehouse (OLDW) cohorts into equal halves for the development and validation in order to have a good representation of health system databases for validation. The OLDW is a longitudinal, real-world data asset with de-identified administrative claims and electronic health record data. Our datasets also included clinical trial cohorts, and we confirmed the results are consistent after excluding these cohorts. Even in those studies that could not share individual-level data, collaborators ran a statistical code specific for the present study and shared relevant estimates and variance-covariance with the CKD-PC Data Coordinating Centre, and thus the present study should be considered as individual-level data meta-analysis.

Using the previously published method,[5, 13] we first developed the 'CKD Add-on' using the development datasets. The CKD Add-on method consists of the following three steps: (i) linear regression models to estimate expected levels of eGFR and log-ACR according to traditional CVD risk factors; (ii) subdistribution hazard ratios (sub-HRs) of CVD outcome for eGFR and log-ACR adjusted for traditional risk factors; and (iii) the calibration of predicted CVD risk based on the deviation between actual eGFR and log-ACR and expected eGFR and log-ACR (from the first step) and their adjusted sub-HRs (from the second step) in every individual. In the first two steps, we included all possible two-way interaction terms with age. One exception was log-ACR in the second step since age did not statistically significantly modify the association of log-ACR with CVD risk ($P = 0.12$). In the second step, log-sub-HRs for traditional CVD risk factors were fixed according to the original SCORE2 or SCORE2-OP coefficients, and eGFR was modelled with two knots at 60 and 90 mL/min/1.73 m^2 to reflect well-known J-shaped associations between eGFR and CVD risk.[2] Since the main purpose of a CKD Add-on is to enhance the predicted risk related to reduced eGFR (but not necessarily high eGFR), we only applied sub-HRs for eGFR below 90 mL/min/1.73 m^2 when we implemented CKD Add-ons. Following the development process of SCORE2 and SCORE2-OP,[8] we used sub-HRs based on Fine and Gray models accounting non-CVD death as a competing outcome. In studies with only data on dipstick proteinuria, we secondarily developed a CKD Add-on for dipstick proteinuria and eGFR. Given that eGFR is more widely available than albuminuria in clinical practice, as we did previously,[5] we developed a CKD Add-on with eGFR only first [expressed as CKD Add-on (eGFR only) below]. Subsequently, we developed a CKD Add-on with eGFR and measures of albuminuria (CKD Add-on [eGFR + ACR] and CKD Add-on [eGFR + dipstick], with the former as our primary Add-on).

Using the validation datasets, we assessed the following prediction statistics after applying CKD Add-ons: Harrel's C-statistic as a measure of risk discrimination[14] and categorical net reclassification improvement (NRI).[15] According to the 2021 ESC guideline,[3] we categorized predicted risk into age-specific categories of low/moderate, high, and very high CVD risk. The corresponding 10-year risk thresholds were 2.5% and 7.5% in age <50 years, 5 and 10% in 50–69 years, and 7.5 and 15% in ≥70 years. We used normal approximations to calculate 95% confidence intervals of C-statistics and NRI. We primarily used the study-specific recalibrated baseline risk of each cohort since the evaluation of the improvement of an established risk equation like SCORE2 is predicated on the assumption that the established equation is well-calibrated in the relevant cohort. We, *a priori,* selected the Clinical Practice Research Datalink (CPRD) for the validation of calibration, since both SCORE2 and SCORE2-OP were well-calibrated in this UK dataset.[8] As done previously,[5] in CKD cohorts, as the expected values of CKD measures, we used the mean of eGFR and albuminuria in each cohort given overestimation of expected eGFR and underestimation of expected ACR when relying on linear regression models from non-CKD cohorts.

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Table 1 Overall baseline characteristics for development and validation datasets

	Development datasets	Validation datasets
Number of datasets	34	34
Number of participants	3 054 840	5 997 719
Age (SD), y	54 (14)	55 (14)
Male sex, %	43	56
Current smokers, %	7.1	19
Systolic BP (SD), mmHg	126 (17)	127 (17)
Diabetes, %	18	18
Total cholesterol (SD), mmol/L	4.8 (0.9)	4.9 (0.9)
HDL cholesterol (SD), mmol/L	1.4 (0.4)	1.3 (0.4)
eGFR (SD), mL/min/1.73 m^2	90 (19)	91 (19)
N for ACR	625 531 (21%)	1 429 373 (26%)
ACR (IQI), mg/g	11 (6–28)	9 (4–29)
N for dipstick	947 323 (36%)	1 229 141 (40%)
Dipstick ≥1+, %	9.1	8.1
Follow-up (SD), y	3.7 (3.6)	4.6 (3.6)
Number of CVD events	90 650	142 379
10-y baseline risk (IQI)[a]		
Men	0.059 (0.031–0.069)	0.050 (0.034–0.064)
Women	0.030 (0.017–0.042)	0.029 (0.021–0.041)
Older men	0.202 (0.128–0.257)	0.155 (0.135–0.206)
Older women	0.141 (0.088–0.174)	0.108 (0.083–0.149)

Values indicated count, proportion, mean (SD), or median (IQI).
[a]Baseline risk was estimated in the 10-year time frame with each predictor centred at age 60 years, systolic blood pressure 120 mmHg, total cholesterol 6 mmol/L, HDL cholesterol 1.3 mmol/L, never smokers, and no diabetes for younger age scenario and 73 years, 150 mmHg, 6 mmol/L, and 1.4 mmol/L for older age scenarios (smoking status and diabetes stayed the same). For cohorts with only 5-year follow-up time, 5-year baseline risk was converted to 10-year by 1-(1-risk)^2. Between-study difference was considerable even within the development or validation datasets, and the IQIs for the baseline risk in the validation studies overlap the estimates in the development datasets.

We conducted additional analyses to evaluate the public health and clinical implications of the CKD Add-ons. First, we described the median ratio of newly predicted risk with a CKD Add-on to originally predicted risk without a CKD Add-on; we took the median and IQI of median ratios from individual datasets. Second, we explored four clinical scenarios with a specific combination of traditional CVD risk factors and described the changes in predicted risk before and after applying a CKD Add-on for two sets of levels of eGFR and ACR representing moderate and severe CKD (eGFR 45 mL/min/1.73 m^2 + ACR 150 mg/g and eGFR 25 mL/min/1.73 m^2 + ACR 500 mg/g, respectively). Finally, we evaluated NRI when we applied SCORE2 or SCORE2-OP, as appropriate, with a CKD Add-on instead of the approaches recommended in the 2021 ESC guideline on CVD prevention (i.e. qualitative classification in moderate and severe CKD and quantitative risk prediction using SCORE2 or SCORE2-OP in mild CKD).

All analyses used complete datasets and were conducted with STATA 16 (College Station, TX). We followed the TRIPOD statement for reporting.[16]

Results

Study characteristics

Development datasets and validation datasets included 3 054 840 individuals and 5 997 719 individuals, respectively. Summary characteristics were largely similar between development and validation datasets, although the proportion of men was greater in the validation datasets than in the development datasets (*Table 1*). Characteristics across individual studies are summarized in Supplementary material online, *Table S1*.

Development of CKD add-ons in the development datasets

The coefficients of traditional CVD risk factors for estimating expected eGFR and log-ACR are displayed in Supplementary material online, *Table S2*. Older age and lower HDL cholesterol were associated with lower baseline eGFR. Higher systolic blood pressure, diabetes, and lower eGFR were the major correlates of higher baseline log-ACR. As anticipated,[2,5] both lower eGFR and higher ACR were significantly associated with elevated CVD risk (*Table 2*), in the context of both SCORE2 and SCORE2-OP. Sub-HR per 15 mL/min/1.73 m^2 lower eGFR below 60 mL/min/1.73 m^2 was greater when we investigated adults aged ≥30 years compared to when we restricted to older adults aged ≥60 years [1.74 (1.64, 1.84) at age 55 vs. 1.33 (1.25, 1.40) at age 75]. Sub-HR for higher ACR was similar regardless of age. Dipstick proteinuria also demonstrated a dose-response relationship with CVD risk. When we excluded a cluster randomized community-level intervention trial in the development datasets, results were almost identical (Supplementary material online, *Table S3*).

We confirmed the improvement in C-statistics with both the CKD Add-on (eGFR only) and the CKD Add-on (eGFR + ACR) in

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

Variables	Sub hazard ratio (95% CI)		Sub hazard ratio (95% CI)
CKD Add-on (eGFR only)	**Age 30+[a]**	**CKD Add-on (eGFR only)**	**Age 60+[b]**
eGFR <60 at age 55, per –15 mL	**1.74 (1.64–1.84)**	eGFR <60 at age 75, per –15 mL	**1.33 (1.25–1.40)**
eGFR 60–89 at age 55, per –15 mL	**1.09 (1.00–1.19)**	eGFR <90 at age 75, per –15 mL	**1.08 (1.05–1.11)**
eGFR 90 + at age 55, per –15 mL	**0.75 (0.70–0.82)**	eGFR 90 + at age 75, per –15 mL	**0.62 (0.52–0.74)**
eGFR <60 × age, per –15 mL × 5y	**0.92 (0.91–0.94)**	eGFR <60 × age, per –15 mL × y	**0.99 (0.98–0.99)**
eGFR 60–89 × age, per –15 mL × 5y	1.01 (0.98–1.03)	eGFR <90 × age, per –15 mL × y	**0.99 (0.98–1.00)**
eGFR 90+ × age, per –15 mL × 5y	0.98 (0.95–1.00)	eGFR 90+ × age, per –15 mL × y	0.99 (0.98–1.01)
CKD Add-on (eGFR + ACR)		**CKD Add-on (eGFR + ACR)**	
ACR, per eight-fold	**1.28 (1.21–1.34)**	ACR, per 8 fold	**1.27 (1.21–1.33)**
CKD Add-on (eGFR + dipstick)		**CKD Add-on (eGFR + dipstick)**	
Trace	**1.30 (1.22–1.39)**	Trace	**1.29 (1.20–1.37)**
+	**1.51 (1.37–1.66)**	+	**1.47 (1.34–1.62)**
++ or more	**1.61 (1.50–1.73)**	++ or more	**1.52 (1.42–1.64)**

Bold indicates statistical significance.
[a]Age 30+, all population including diabetes and no diabetes (in the context of SCORE2).
[b]Age 60+, all population including diabetes and no diabetes (in the context of SCORE2-OP).

the development datasets in the context of both SCORE2 and SCORE2-OP (see Supplementary material online, *Table S4*). For example, in the study population aged ≥30 years, the CKD Add-on (eGFR only) and the CKD Add-on (eGFR + ACR) for SCORE2 improved C-statistic by 0.004 (0.003–0.006) and 0.015 (0.011–0.019), respectively. Similarly, the CKD Add-on (eGFR only) and the CKD Add-on (eGFR + ACR) for SCORE2-OP demonstrated C-statistic improvement (0.008 [0.006–0.010] and 0.022 [0.016–0.027], respectively) in the study population aged ≥60 years. We also observed positive overall NRIs in all comparisons with the CKD Add-on (eGFR only) and the CKD Add-on (eGFR + ACR) (see Supplementary material online, *Table S3*). The CKD Add-on (eGFR + dipstick) also improved risk prediction. Results across individual datasets are shown in Supplementary material online, *Tables S5 and S6* [CKD Add-on (eGFR only)] and Supplementary material online, *Tables S7 and S8* [CKD Add-on (eGFR + ACR)].

Validation of CKD add-ons in the validation datasets

Both the CKD Add-on (eGFR only) and the CKD Add-on (eGFR + ACR) improved C-statistics in the target populations for SCORE2 and SCORE2-OP in the validation datasets (*Table 3*). In the study population aged 40–69 years without diabetes, the CKD Add-on (eGFR only) and the CKD Add-on (eGFR + ACR) for SCORE2 improved C-statistic by 0.006 (0.004–0.008) and 0.016 (0.010–0.023), respectively. The corresponding estimates of the CKD Add-on (eGFR only) and the CKD Add-on (eGFR + ACR) for SCORE2-OP were 0.012 (0.09, 0.015) and 0.024 (0.014, 0.035) in the study population aged 70 years or older without diabetes. Overall NRI was also significantly positive in all comparisons (e.g. 0.039 [0.018–0.059] with the CKD Add-on [eGFR + ACR] for SCORE2). The CKD Add-on (eGFR + dipstick) also improved the risk prediction (*Table 3*). The results were largely consistent when we focused on individuals at high risk of CVD, as defined in the ESC 2021 CVD prevention guideline[3] and noted above (see Supplementary material online, *Table S9*). The improvement of risk prediction was generally more evident when we included individuals with diabetes (see Supplementary material online, *Table S10*) as well as when we removed the two clinical trials in individuals with diabetes from the analyses (see Supplementary material online, *Table S11*). The vast majority of individual studies demonstrated improvement in C-statistic and positive NRIs with the CKD Add-on (eGFR only) (see Supplementary material online, *Tables S12 and S13*) and the CKD Add-on (eGFR + ACR) (see Supplementary material online, *Tables S14 and S15*). When we focused on general population cohorts, the results were largely consistent (see Supplementary material online, *Table S16*). In CPRD, the application of the CKD Add-on (eGFR only) or the CKD Add-on (eGFR + ACR) did not alter the calibration of SCORE2 and SCORE2-OP much (Supplementary material online, *Figure S1*).

Implications of CKD add-ons

The median predicted risk ratio (i.e. with a CKD Add-on over without a CKD Add-on) across the validation datasets by different stages of CKD is shown in *Figure 1*. In the study population aged 40–69 without diabetes, the median predicted risk ratio was ∼2.8 in severe CKD (cross-categories of eGFR and ACR in red in *Figure 1*), ∼1.7 in moderate CKD (cross-categories in orange), and ∼1.3 in mild CKD (cross-categories in yellow). The corresponding ratios were ∼1.6, ∼1.3 and ∼1.1 in the study population aged ≥70 years without diabetes. We observed largely similar patterns for the CKD Add-on with dipstick (Supplementary material online, *Figure S2*). The results were similar in the study population including diabetes (see Supplementary material online, *Figure S3*). *Figure 2* demonstrates the extent to which the CKD Add-on (eGFR + ACR) influences predicted risk based on SCORE2 and SCORE2-OP in a few hypothetical scenarios (details in see Supplementary material online, *Appendix S1*).

In 13 European datasets in CKD-PC including 57 485 participants with CKD, according to the approach in the 2021 ESC CVD prevention guideline (i.e. qualitative classification of severe and moderate

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Table 3 C-statistics and NRI with the CKD Add-ons in the SCORE2 and SCORE2-OP populations from the validation datasets

		CKD Add-on (eGFR only)	CKD Add-on (eGFR + ACR)	CKD Add-on (eGFR + dipstick)
Overall		**SCORE2 in age 40–69, non-diabetics population**		
N		2 817 487	510 622	684 170
Base C-statistic (IQI)		0.686 (0.658–0.719)	0.634 (0.604–0.697)	0.688 (0.671–0.715)
ΔC-statistic (95% CI)		0.006 (0.004–0.008)	0.016 (0.010–0.023)	0.019 (0.013–0.025)
Category NRI (95% CI)	**Overall**	0.030 (0.023–0.037)	0.039 (0.018–0.059)	0.095 (0.071–0.120)
	Event	0.050 (0.039–0.060)	0.104 (0.069–0.139)	0.124 (0.093–0.154)
	Non-event	–0.012 (–0.014 to –0.010)	–0.041 (–0.053 to –0.029)	–0.027 (–0.034 to –0.021)
Overall		**SCORE2-OP in age 70+, non-diabetics population**		
N		556 887	57 696	121 312
Base C-statistic (IQI)		0.641 (0.601–0.656)	0.613 (0.568–0.661)	0.640 (0.626–0.670)
ΔC-statistic (95% CI)		0.012 (0.009–0.015)	0.024 (0.014–0.035)	0.024 (0.017–0.031)
Category NRI (95% CI)	**Overall**	0.033 (0.024–0.042)	0.046 (0.019–0.074)	0.068 (0.044–0.093)
	Event	0.088 (0.065–0.111)	0.150 (0.101–0.200)	0.214 (0.165–0.262)
	Non-event	–0.044 (–0.057 to –0.032)	–0.077 (–0.100 to –0.055)	–0.146 (–0.191 to –0.100)

C-statistic was calculated within each gender group, no comparison between men and women.
Risk category was defined as low/moderate risk (<2.5% for age <50, <5% for age 50–69 and <7.5% for age 70+), high risk (2.5–7.5% for age <50, 5–10% for age 50–69 and 7.5–15% for age 70+), very high risk (>7.5% for age <50, >10% for age 50–69 and >15% for age 70+).

	CKD stages risk heat map				In validation datasets	SCORE2 population (age 40-69, no diabetes	SCORE2-OP population (age 70+, no diabetes)
	ACR					Risk ratio of CKD Add-on (eGFR+ACR) to SCORE2	Risk ratio of CKD Add-on (eGFR+ACR) to SCORE2-OP
eGFR	<30	30-299	300+		CKD Stages		
90+					Risk ratio, Median (IQI)		
60-89					No CKD	0.98 (0.97, 1.00)	0.97 (0.93, 0.99)
45-59					CKD at moderate risk	1.29 (1.24, 1.30)	1.15 (1.11, 1.17)
30-44					CKD at high risk	1.70 (1.63, 1.74)	1.29 (1.23, 1.34)
<30					CKD at very high risk	2.78 (2.59, 3.05)	1.60 (1.38, 1.65)
					Overall	1.03 (1.00, 1.07)	1.04 (0.99, 1.07)

Figure 1 Chronic kidney disease staging and risk ratio of the chronic kidney disease add-on (estimated glomerular filtration rate + albumin-to-creatinine ratio) in the SCORE2 and SCORE2-OP populations from the validation datasets.

CKD to very-high and high CVD risk and SCORE2 or SCORE2-OP in mild CKD), the proportion of individuals in the CVD risk of low/moderate, high, and very-high was 40.9%, 38.0%, and 21.2%, respectively. The corresponding proportion was 44.2%, 35.5%, and 20.3% when using a CKD Add-on. Compared to the approach in the 2021 ESC guideline, the new approach of calibrating SCORE2/SCORE2-OP with a CKD Add-on in this CKD population in Europe resulted in 13.8% (4524 out of32 703) of the individuals reclassified upward to a higher CVD risk group and 14.6% (4788 out of32 703) downward to a lower risk group, with overall positive NRI in the study populations aged 40–69 years [0.100 (0.062–0.138)] and ≥70 years [0.063 (0.014–0.112)] (see Supplementary material online, *Table S17*).

Discussion

Using data from >9 million individuals from 68 datasets, we have developed and validated CKD Add-ons for SCORE2 and SCORE2-OP, the latest risk algorithms designed for primary CVD prevention in Europe.[8] The improvement of risk prediction was generally greater with the CKD Add-on (eGFR + ACR) than the CKD Add-on (eGFR only). For example, in the target population of SCORE2 (age 40–69 years without diabetes) in the validation datasets, increases in C-statistics were 0.017 (95%CI 0.011–0.023) vs. 0.007 (0.005–0.008), respectively. NRI also supported the risk prediction improvement with either CKD Add-on. The improvement in risk prediction with the CKD Add-on was confirmed when we used dipstick proteinuria instead of ACR, included populations with diabetes, and focused on the high CVD risk group.

It is not easy to appreciate clinical values of specific risk prediction models from changes in C-statistics or NRI, and thus we have comprehensively evaluated other matrices such as a ratio of the predicted risk after an Add-on to the originally predicted risk, which demonstrated the impact of accounting (or not accounting) for the CKD measures. For example, in the target population of SCORE2, the median ratio in our validation datasets was ~1.7 in moderate CKD (e.g. eGFR 45–59

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	Patient A		Patient B		Patient C		Patient D	
European low risk region	Predicted risks, %	CVD risk classification	Predicted risks, %	CVD risk classification	Predicted risks, %	CVD risk classification	Predicted risks, %	CVD risk classification
Original CVD risk	2.0	Low/Moderate	1.6	Low/Moderate	4.5	Low/Moderate	8.8	High
eGFR 45 + ACR 150	6.1	High	4.3	Low/Moderate	10	Very high	16	Very high
eGFR 25 + ACR 500	16	Very high	9.4	High	18	Very high	22	Very high
European moderate risk region								
Original CVD risk	2.5	Low/Moderate	1.9	Low/Moderate	5.8	High	12	High
eGFR 45 + ACR 150	7.7	Very high	5.1	High	13	Very high	20	Very high
eGFR 25 + ACR 500	20	Very high	11	Very high	23	Very high	28	Very high
European high risk region								
Original CVD risk	2.6	High	2.4	Low/Moderate	6.0	High	18	Very high
eGFR 45 + ACR 150	8.0	Very high	6.5	High	14	Very high	31	Very high
eGFR 25 + ACR 500	21	Very high	14	Very high	23	Very high	42	Very high
European very high risk region								
Original CVD risk	4.7	High	5.1	High	11	Very high	31	Very high
eGFR 45 + ACR 150	14	Very high	13	Very high	24	Very high	50	Very high
eGFR 25 + ACR 500	35	Very high	28	Very high	39	Very high	64	Very high
Patient A: Age 42 man, current smoker, SBP 128, no DM, total cholesterol 3.8, HDL-C 1.4								
Patient B: Age 52 woman, not current smoker, SBP 128, no DM, total cholesterol 4.5, HDL-C 1.2								
Patient C: Age 62 man, not current smoker, SBP 128, no DM, total cholesterol 4.5, HDL-C 1.6								
Patient D: Age 72 woman, no current smoker, SBP 148, no DM, total cholesterol 3.8, HDL-C 1.6								

CVD risk classification was defined as low/moderate risk (<2.5% for age <50, <5% for age 50-69 and <7.5% for age 70+), high risk (2.5-7.5% for age <50, 5-10% for age 50-69 and 7.5-15% for age 70+), very high risk (>7.5% for age <50, >10% for age 50-69 and >15% for age 70+).

Figure 2 The chronic kidney disease add-on (estimated glomerular filtration rate + albumin-to-creatinine ratio) impact on predicted risk based on SCORE2 and SCORE2-OP in four hypothetical scenarios. Cardiovascular disease risk classification was defined as low/moderate risk (<2.5% for age <50, <5% for age 50–69 and <7.5% for age 70+), high risk (2.5–7.5% for age <50, 5–10% for age 50–69 and 7.5–15% for age 70+), very high risk (>7.5% for age <50, >10% for age 50–69 and >15% for age 70+).

mL/min/1.73 m^2 plus ACR 30–299 mg/g) and ~2.8 in severe CKD (e.g. eGFR 30–44 mL/min/1.73 m^2 plus ACR 300 + mg/g). The corresponding ratios were slightly smaller in the targeted population for SCORE2-OP, ~1.3 and ~1.6, respectively. Importantly, in both target populations, the ratio was ~1 in individuals without CKD, confirming that those without CKD can simply rely on SCORE2 or SCORE2-OP. Of note, in CKD populations from 13 European cohorts, SCORE2 or SCORE2-OP with a CKD Add-on demonstrated a better risk classification than the quantitative approach proposed in the ESC 2021 CVD prevention guideline.

The discussion of the value of a novel predictor intrinsically includes the concept of whether that predictor should be newly measured or not. However, the situation of CKD measures is quite different in this regard since the assessment of eGFR and albuminuria is already recommended in several clinical scenarios. In fact, in the US, serum creatinine is measured ~300 million times annually.[17] Likewise, the evaluation of albuminuria is recommended in patients with diabetes, hypertension, and reduced eGFR. Thus, in many individuals, the data on these CKD measures are readily available, and their omission is a critical missed opportunity to further personalize risk prediction and prevention approaches of CVD. Therefore, our CKD Add-ons would provide a validated means for clinicians and patients to incorporate existing CKD measures into SCORE2 algorithms and further personalize CVD preventive therapies.

A few recent studies have shown that measures of albuminuria are less likely to be assessed compared to eGFR even when it is clinically indicated (e.g. patients with diabetes or hypertension). For example, in a US clinical database study, eGFR was measured at least once in a 1-year period among most patients with diabetes, whereas only half of them had measures of albuminuria.[18] Our data further support the importance of taking into account albuminuria for CVD risk assessment. Importantly, the present study has validated a CKD Add-on using dipstick proteinuria as well for improving risk prediction of CVD, which adds to the applicability of our findings.

Several limitations of the present study should be acknowledged. The assessment of eGFR, albuminuria, and traditional CVD predictors and the ascertainment of CVD events were not necessarily standardized across all the cohorts. In addition, the data availability of albuminuria in clinical database cohorts is limited to a subsample, reflecting clinical indications. However, the overall consistent results across most of the cohorts, with diverse demographic and clinical characteristics, support the robustness of our study. Also, although we included 13 datasets from Europe, all are from low- or moderate-risk regions. Also, we have not included information on primary causes of CKD.

In conclusion, our CKD Add-ons improved CVD risk prediction according to SCORE2 and SCORE2-OP. This approach will help clinicians and patients refine risk prediction and further personalize preventive therapies for CVD when information on the CKD measures is available and indicates CKD.

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Authors' contributions

K.M. and Y.S. 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., S.K., S.H.J.H., Y.S., S.H.B., M.E.G., F.L.J.V., L.P., 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. K.M., S.K., S.H.J.H., Y.S., S.H.B., M.E.G., F.L.J.V., L.P., and J.C. drafted the manuscript. All the authors contributed to the analysis and interpretation of data and to the critical revision of the manuscript for important intellectual content as well as the final decision to submit for publication. 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.

Supplementary material

Supplementary material is available at European Journal of Preventive Cardiology online.

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Data availability

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).

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