Development of Risk Prediction Equations for Incident Chronic Kidney Disease

Running title: Predicting Chronic Kidney Disease

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Key Points:

Question: Can development of chronic kidney disease be predicted using readily available demographic, clinical, and laboratory variables?

Findings: In this analysis of 5,222,711 individuals in 34 multinational cohorts from 28 countries, 5-year risk prediction equations for CKD were developed and demonstrated high discrimination (median C-statistic for the equation for people without diabetes, 0.85; median C-statistic for the equation for people with diabetes, 0.80) and variable calibration (69% of the study populations had a slope of observed to predicted risk between 0.80 and 1.25). Discrimination and calibration were similar in 9 external cohorts consisting of 2,253,540 people.

Meaning: Equations for predicting risk of incident chronic kidney disease were developed in over 5 million people from 34 multinational cohorts and demonstrated high discrimination and variable calibration in diverse populations.

ABSTRACT

IMPORTANCE - Early identification of individuals at elevated risk of developing chronic kidney disease could improve clinical care through enhanced surveillance and better management of underlying health conditions.

OBJECTIVE – To develop assessment tools to identify individuals at increased risk of chronic kidney disease, defined by reduced estimated glomerular filtration rate (eGFR).

DESIGN, SETTING, AND PARTICIPANTS – Individual level data analysis of 34 multinational cohorts from the CKD Prognosis Consortium including 5,222,711 individuals from 28 countries. Data were collected from April, 1970 through January, 2017. A two-stage analysis was performed, with each study first analyzed individually and summarized overall using a weighted average. Since clinical variables were often differentially available by diabetes status, models were developed separately within participants with diabetes and without diabetes. Discrimination and calibration were also tested in 9 external cohorts (N=2,253,540).

EXPOSURE Demographic and clinical factors.

MAIN OUTCOMES AND MEASURES – Incident eGFR <60 ml/min/1.73 m^2.

RESULTS – In 4,441,084 participants without diabetes (mean age, 54 years, 38% female), there were 660,856 incident cases of reduced eGFR during a mean follow-up of 4.2 years. In 781,627 participants with diabetes (mean age, 62 years, 13% female), there were 313,646 incident cases during a mean follow-up of 3.9 years. Equations for the 5-year risk of reduced eGFR included age, sex, ethnicity, eGFR, history of cardiovascular disease, ever smoker, hypertension, BMI, and albuminuria. For participants with diabetes, the models also included diabetes medications, hemoglobin A1c, and the interaction between the two. The risk equations had a median C statistic for the 5-year predicted probability of 0.845 (25^{th} – 75^{th} percentile, 0.789-0.890) in the cohorts without diabetes and 0.801 (25^{th} – 75^{th} percentile, 0.750-0.819) in the cohorts with diabetes. Calibration analysis showed that 9 out of 13 (69%)

study populations had a slope of observed to predicted risk between 0.80 and 1.25. Discrimination was similar in 18 study populations in 9 external validation cohorts; calibration showed that 16 out of 18 (89%) had a slope of observed to predicted risk between 0.80 and 1.25.

CONCLUSIONS AND RELEVANCE – Equations for predicting risk of incident chronic kidney disease developed in over 5 million people from 34 multinational cohorts demonstrated high discrimination and variable calibration in diverse populations.

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem that is associated with major adverse health events, including kidney failure, cardiovascular disease, and death. The Global Burden of Disease study estimates that nearly 697 million persons worldwide had reduced estimated glomerular filtration rate (eGFR) or increased albuminuria in 2016, an increase of 70% since 1990.[1] Globally, years of life lost due to CKD increased by 53% in the same period.[1] CKD is the 16th most common cause of years of life lost.[2] Factors associated with the increased prevalence of CKD include the aging of the population and the increasing prevalence of diabetes, hypertension, and obesity. The ability to identify people at risk for CKD may prevent adverse health outcomes associated with CKD. Moreover, even in those who are diagnosed with CKD, proper management may be hindered by lack of awareness of CKD and its management among clinicians and uncertainties about the underlying risk of CKD progression.

A kidney failure risk equation may help improve care for patients with established CKD,[3,4] but relatively little work has been performed to develop predictive tools to identify those at increased risk for *developing* CKD, defined by reduced eGFR, despite the high lifetime risk of CKD, which is estimated to be 59.1% in the United States.[3] A simple risk assessment tool that helps clinicians quickly identify patients at increased risk of reduced eGFR and provides an estimate of the magnitude of risk for reduced eGFR could lead to better and more targeted surveillance strategies and potentially to better management of the factors associated with reduced eGFR. In the present study, data from multinational cohorts were used to develop and evaluate risk prediction equations for CKD defined by reduced eGFR.

METHODS

This study was approved for use of deidentified 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.

Participating cohorts

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) includes study cohorts worldwide that were identified from the general population and from patients at high risk of cardiovascular disease (**eAppendix 1**).[4-9] Inclusion criteria required that cohorts included at least 1,000 participants, data on serum creatinine and albuminuria, and 50 or more events of the outcome of interest. Included cohorts consisted of prospective studies, clinical trials, and administrative healthcare datasets. Separate risk models were developed for those with and without diabetes mellitus. The analyses among participants without diabetes included 31 cohorts, and the analyses among participants with diabetes included 15 cohorts. Within cohorts, eligible participants were aged ≥18 years old with an eGFR >60 ml/min/1.73 m^2 at baseline. Eligible participants had no previous end-stage kidney disease and had at least one serum creatinine value during follow-up. Because the prevalence and incidence of CKD differ by race/ethnicity, data on race and ethnicity were analyzed from the participating cohorts. Methods used to determine race varied from cohort to cohort, but most cohorts used self-report to define race and ethnicity. Data were collected from April, 1970 through January, 2017.

Procedures

The CKD-EPI creatinine equation was used to calculate eGFR.[10] In cohorts where the creatinine measurement was not standardized to isotope dilution mass spectrometry (IDMS), values were multiplied by 0.95 before eGFR calculation.[11] 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 ≥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. Smoking was classified as ever smoking vs. never smoking. Participants with a history of myocardial infarction, coronary revascularization, heart failure, or stroke were considered to have a history of cardiovascular disease. Measures of albuminuria were restricted to the urine albumin-to-creatinine ratio. Among participants with diabetes, hemoglobin A1c, oral diabetes medications, and insulin use at baseline were also recorded.

Outcomes

The outcome of interest was incident eGFR <60 ml/min/1.73 m^2. Additional outcomes were eGFR <45 ml/min/1.73 m^2, eGFR <30 ml/min/1.73 m^2, and 40% decline in eGFR. Participants who developed end-stage kidney disease, mostly identified by procedure codes or by linkage to national registries before a qualifying outpatient level of eGFR were also considered to have developed the outcome of interest. In secondary analyses, we evaluated the risk of confirmed outcomes. Outcomes were defined as confirmed if there were at least three measures of eGFR (one baseline, two during follow-up) and the first eGFR below the threshold was confirmed by a second qualifying eGFR between 90 days and 2 years later, or if the linear slope of eGFR decline crossed the threshold during follow-up (**eAppendix 1**). In both cases, the event date was considered the date of the first qualifying eGFR measurement.

Prediction Model Development

The prediction model was built from weighted-average hazard ratios estimated in all participating cohorts and an adjusted baseline risk estimated in cohorts with frequent outcome assessment. To estimate the hazard ratios, each study was first analyzed individually, then combined, weighting the study by the square-root of the number of events in each cohort and capped at 5-times the median study weight. This method was used to ensure that the largest studies did not dominate the analysis due

to small within-study variance compared to total variance. We performed complete case analysis, excluding variables which were missing more than 50% of the time in cohort-specific analyses. Since variables were often differentially available by diabetes status (e.g., albuminuria, hemoglobin A1c; missing data shown in **eTable 1A and B**), models were developed separately for participants with diabetes and without diabetes. The primary model included demographic variables (age, sex, ethnicity), eGFR (linear splines with knot at 90 ml/min/1.73 m^2), history of cardiovascular disease, ever smoker, hypertension, BMI, and albuminuria. The primary model for participants with diabetes also included diabetes medications (insulin vs. only oral medications vs. none), hemoglobin A1c, and the interaction between the two.

The albuminuria variable was handled differently for those with vs. without diabetes. For the model among participants with diabetes, missing albuminuria was treated as a dummy variable with reference at a urine albumin-to-creatinine ratio of 10 mg/g. For the model among participants without diabetes, where albuminuria was available only in a minority of individuals, a patch approach was used.[12] Models were fit in all the cohorts using all variables except albuminuria, and data were combined as described above. The weighted average coefficients were then held constant in cohort-specific models among participants with measures of albuminuria to obtain a conditional coefficient for albuminuria, which was then combined for analyses using the weighting described above. This conditional, weighted average coefficient for albuminuria was applied to the observed level of albuminuria less the expected level of albuminuria (**eTable 2**) and combined with the weighted-average coefficients for the other variables in the final model.

To obtain the adjusted baseline risk for use with the primary model, we held the weighted-average coefficients constant and fit a multivariable competing risk model in the studies with follow-up for

mortality and mean time between creatinine measures of less than one year. The adjusted sub-hazard was smoothed using a Weibull distribution and the mean was estimated using weights determined by the method described above. The prediction model then combined the mean adjusted baseline risk with the weighted-average coefficients.

Evaluation of Model Performance

To evaluate model discrimination, Harrell's C-statistic was estimated within each cohort and summarized as the median and interquartile range across studies. Model calibration was plotted using observed versus predicted risk per decile of predicted risk at 5 years in each cohort with frequent measures of creatinine (median time between two measurements was approximately 1 year or less and mean follow-up time was at least two years) and quantified using a regression of the deciles of mean observed risk on the mean predicted risk in a zero-intercept linear regression model. Calibration was assessed by visual inspection of the plots (dots showing deciles are close to identity line) and by the slope of observed to predicted risk being near to 1.[13] To summarize calibration, we determined the number of study populations with an observed risk within 1.25-fold that of the predicted risk (i.e., with a slope between 0.80 and 1.25 (1/0.8)). These metrics of discrimination and calibration were also calculated within 9 external validation cohorts selected from OptumLabs® Data Warehouse. **eAppendix 1** describes the methods for selecting centers for the nine external validation cohorts. The OptumLabs Data Warehouse contains deidentified longitudinal health information on patients receiving care in health systems participating in the OptumLabs collaborative research and innovation center in the U.S. The database includes people ages 18 to 88 years, from diverse ethnicities and geographical regions across the United States (**eTable 3**). The electronic health record (EHR)-derived data include a subset of EHR data that have been normalized and standardized across health systems into a single database, including information on demographics, laboratory values, encounter and discharge codes.[14]

To compare the newly developed models to existing equations, predicted risks using the newly developed models were compared with risks calculated using two published equations identified in a recent review [15] (herein referred to as the Chien equation[16] and the O'Seaghdha equation[17], respectively **eAppendix 4**). The Chien equation was developed in 5,168 Chinese individuals who underwent baseline health examinations at the National Taiwan University Hospital[16] and annual follow-up examinations that included measurements of serum creatinine concentration for assessing the outcome of reduced eGFR. During a median follow-up of 2.2 years, 190 individuals developed CKD. We used the Chien clinical equation, which included age, body mass index, diastolic blood pressure, and history of type 2 diabetes and stroke. The O'Seaghdha prediction model was developed in the predominantly white population of Framingham, Massachusetts, using baseline serum creatinine and a subsequent measure 10 years later. Among the 2,490 individuals aged 45-64 years included in this study, 229 developed eGFR <60 ml/min/1.73m^2 at 10 years. The O'Seaghdha model included age, hypertension, diabetes, eGFR category, and albuminuria .[17]

The performance of the newly developed model, the Chien equation, and the O'Seaghdha equation were compared in the CKD-PC cohorts that provided individual-level participant data and had the required variables for all equations. Differences in C-statistics were estimated within all cohorts and then summarized using random-effects meta-analysis. Brier scores, the mean squared difference between the predicted risk vs observed binary outcomes, were used to evaluate which risk equation showed the best calibration within each cohort (**eAppendix 4**).[18] Brier scores were assessed only within the subset of cohorts with frequent assessments of creatinine. Comparisons of the discrimination and calibration were also performed within the 9 external validation cohorts from OptumLabs Data Warehouse.

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.

RESULTS

Overall, 5,222,711 participants were included (**eTable 4**), of whom 781,627 (15.0%) had diabetes. Baseline characteristics of participants in the 34 individual cohorts are shown in **Table 1** according to the presence or absence of diabetes. The population without diabetes had a mean age of 54 years (SD, 16) and 38% were female. The population with diabetes had a mean age of 62 years (SD, 11) and 13% were female, owing primarily to the Veterans Administration cohort, which was 97% male.

Among the 4,441,084 participants without diabetes, there were 660,856 (14.9%) incident cases of eGFR <60 ml/min/1.73m^2 during a mean follow-up of 4.2 years, and 374,513 (56.7%) of them were confirmed by subsequent eGFR measurements. Among the 781,627 participants with diabetes, there were 313,646 (40.1%) incident cases during a mean follow-up of 3.9 years, and 212,246 (67.7%) of them were confirmed by subsequent eGFR measurements. The number of participants and the total and confirmed number of events of incident reduced eGFR in the nondiabetic and diabetic cohorts are shown in **eTable 5**.

Risk factors for reduced eGFR

Weighted-average sub-hazard ratios of major risk factors for incident eGFR <60 ml/min/1.73m^2 are shown in **Table 2** and for other eGFR thresholds in **eTable 6** according to the presence or absence of diabetes. Older age, female sex, black race, hypertension, history of cardiovascular disease, lower eGFR, and higher urine albumin-to-creatinine ratio were each significantly associated with incident eGFR <60

ml/min/1.73m^2 in both the diabetic and nondiabetic cohorts. Smoking was significantly associated with incident eGFR <60 ml/min/1.73m^2 only in the nondiabetic cohorts, and elevated hemoglobin A1c and presence and type of diabetes medicines were significantly associated with incident eGFR <60 ml/min/1.73m^2 in the diabetic cohorts.

Discrimination

Measures of discrimination for the 5-year predicted probability of incident eGFR <60 ml/min/1.73m^2, based on the predictive models, are shown separately for the nondiabetic and diabetic cohorts in **eTable 7A.** The median C statistic for the 5-year predicted probability of all eGFR events <60 ml/min/1.73m^2 was 0.845 (25th – 75th percentile, 0.789-0.890) in the cohorts without diabetes and 0.801 (25th – 75th percentile, 0.750-0.819) in the cohorts with diabetes, reflecting good discrimination. For confirmed eGFR events <60 ml/min/1.73m^2, the median C statistic was 0.869 (25th – 75th percentile, 0.823-0.897) in the cohorts without diabetes and 0.808 (25th – 75th percentile, 0.794-0.836) in the cohorts with diabetes. Measures of discrimination for the lower incident eGFR thresholds are shown in **eTable 7B**.

Predicted absolute risk

Adjusted baseline sub-hazards for eGFR <60 ml/min/1.73m^2 were computed over time in nondiabetic and diabetic cohorts with frequent measures of creatinine using baseline covariates from the cohorts and weighted-average coefficients from the models (**Figure 1**). The figure illustrates the variability in the adjusted absolute risk across the cohorts that was unexplained by the covariates included in the models. Similar findings are shown for the lower incident eGFR thresholds in **eFigure 1** for the nondiabetic cohorts and **eFigure 2** for the diabetic cohorts.

Equations for the 5-year predicted risk of incident eGFR<60 ml/min/1.73m^2, based on the predictive models and the mean baseline sub-hazards, are shown separately for individuals with or without diabetes in **eTable 8** and are available online at http://ckdpcrisk.org/ckdrisk**.** The predicted 5-year absolute risk of incident eGFR<60 ml/min/1.73m^2 in individuals without and with diabetes at three ages and for various combinations of risk factors are shown in **Figure 2** and in greater detail for all three incident eGFR thresholds in **eTables 9** and **10**. A wide range of risk was seen, and the level of risk was strongly associated with the demographic features and co-morbid conditions. The absolute risk was generally higher in persons with diabetes than in those without and increased with age regardless of the presence or absence of diabetes. Elevated albuminuria was also significantly associated with the absolute risk regardless of the presence or absence of diabetes. The 5-year absolute risk for confirmed eGFR reduction followed the same pattern as for the unconfirmed endpoint, with lower absolute risk for the confirmed endpoints (**eTables 9** and **10**). Equations for the 5-year predicted risk of other outcomes are shown in **eTables 11** and **12**.

Calibration

Model calibration was assessed visually by plotting observed versus predicted risk per decile of predicted risk at 5 years in the cohorts with frequent measures of creatinine. Plots for the eGFR <60 ml/min/1.73m^2 endpoint are shown in e**Figure 3** and for the lower eGFR endpoints in **eFigures 4** and **5**. The plots reflected the performance of the equations for the primary endpoint in the cohorts, with 9 of the 13 (69%) study populations showing a slope of observed to predicted risk between 0.80 and 1.25 (**eTable 13**). Calibration was generally better for the eGFR <60 ml/min/1.73m^2 endpoint compared to the lower eGFR endpoints, where it was poor in some cohorts (**eTables 14-15**). For example, for eGFR <45 ml/min/1.73 m^2, just 5 of 13 (38%) study populations showed a slope between 0.80 and 1.25. For

eGFR <30 ml/min/1.73 m^2, just 4 out of 11 (36%) study populations showed a slope between 0.80 and 1.25. Calibration, by design, was best in the development cohorts with the highest number of events.

External validation

Model discrimination was tested in 18 study populations in 9 external validation cohorts (N=2,253,540, **eTable 16**). There were 288,462 events over 4.1 years of follow-up in the population without diabetes and 78,697 events over 3.5 years of follow-up in the population with diabetes. Discrimination was similar to that observed in the development cohorts. The median C statistic for the 5-year predicted probability of all eGFR events <60 ml/min/1.73m^2 was 0.84 (25^{th} – 75^{th} percentile, 0.83-0.87) in the population without diabetes and 0.81 (25^{th} – 75^{th} percentile, 0.80-0.82) in the population with diabetes (**eTable 17**). Calibration analysis showed that 16 out of 18 (89%) study populations with a slope between 0.80 and 1.25 (**eFigure 6**, **eTable 18**). Discrimination and calibration for the lower eGFR endpoints are shown in **eFigures 7-8** and **eTables 17-18**. For example, for eGFR <45 ml/min/1.73 m^2, 15 out of 18 (83%) of study populations showed a slope between 0.80 and 1.25. For eGFR <30 ml/min/1.73 m^2, 11 out of 18 (61%) study populations showed a slope between 0.80 and 1.25. Differences in calibration could not be explained by differences in mean baseline characteristics in the underlying study populations.

Comparison to existing equations

The newly developed model for eGFR <60 ml/min/1.73m^2 in the absence of diabetes had better discrimination than the Chien equation (random-effects meta-analyzed difference in C statistic, 0.094, 95% CI: 0.071-0.117) and the O'Seaghdha equation (random-effects meta-analyzed difference in C statistics, 0.020, 95% CI: 0.015-0.025) when compared in the CKD-PC cohorts. Similarly, the Brier score was lower using the newly developed equation in the cohorts with frequent measures of creatinine,

indicating superior calibration for the newly developed equation (**eTable 19**). In the presence of diabetes, the newly developed model had better discrimination than the Chien equation (random-effects meta-analyzed difference in C statistic, 0.107, 95% CI: 0.087-0.128) and the O'Seaghdha equation (random-effects meta-analyzed difference in C statistics, 0.037, 95% CI: 0.030-0.044) and lower Brier scores in two out of three cohorts with frequent measures of creatinine. When evaluated in the 9 external validation cohorts, model discrimination and calibration were also better using the newly developed equations compared to the Chien and O'Seaghdha equations (**eTable 20**).

DISCUSSION

Risk prediction models were developed that facilitated prediction of the 5-year probability of reduced eGFR in diverse populations of men and women with variable ages and ethnicity. Models were developed separately for people with vs. without diabetes. Readily available demographic, clinical, and laboratory variables were used in these risk models, so that risk calculators from these models could conceivably be added to electronic health records to identify patients at increased risk for developing reduced eGFR. Further study is needed to determine whether these risk equations can improve care. For example, future study could assess whether focusing resources on patients at highest risk of developing chronic kidney disease improves blood pressure control and/or weight loss. Future study might also determine whether prescribing medications to improve albuminuria or control diabetes might prevent occurrence of reduced eGFR in those at risk.

Several prediction models of CKD exist for use in the general population.[16,17,19,20] Equations previously developed to identify people at risk for incident eGFR <60 ml/min/1.73m^2 included the Chien equation and the O'Seaghdha equation, both of which have been externally validated.[15-17] External validation of the Chien clinical model was previously done in 3,205 Chinese adults from the Chin-Shan Community

Cardiovascular Cohort. Moderate discrimination was observed for the clinical prediction model in the development cohort (c-statistic = 0.77), but the discriminatory power of the model was greatly reduced in the external validation cohort (c-statistic = 0.67).[16] The O'Seaghdha risk score was validated in 1,777 individuals from the ARIC study (c-statistic = 0.79 in Framingham and 0.74 in ARIC).[17] These prior studies did not develop separate equations for those with vs. without diabetes. The present study, which developed scores separately for people with vs. without diabetes, demonstrated higher C-statistics and better calibration than both the clinical Chien and the O'Seaghdha equations. This was true in the CKD-PC cohorts used in development of the equations as well as in the 9 external validation cohorts.

Risk prediction models that estimate the absolute risk of specific adverse health outcomes have become increasingly popular clinical decision-making tools in recent years, and novel approaches to analyzing existing data are emerging that may enhance prediction.[21] Several models have been developed for estimating the risk of prevalent and incident CKD and end-stage kidney disease,[4,16,17,19,20,22-24] but even those with good discriminative performance have not always performed well in cohorts of people outside the original derivation cohort.[15] In our study, we show that the incidence of low eGFR varies across settings, even after adjustment for variable distribution of risk factors, providing an explanation for differences in calibration in prior studies.

Calibration is an essential aspect of risk prediction, particularly when absolute risk thresholds are used to drive clinical care. A tool that overestimates risk may result in unnecessary treatment, whereas one that underestimates risk may delay optimal management. By design, calibration in the development cohorts in our study was set to the overall weighted risk. Hence, we focused on calibration on external cohorts for an unbiased assessment. Surprisingly, in external validation in over 2 million people, model calibration was even better than that in the development cohorts, suggesting that it may generalize well

394 to US electronic health systems like those represented in OptumLabs Data Warehouse. Other strengths
395 of this study include the large sample sizes of the nondiabetic and diabetic cohorts, and the broad
396 clinical, geographic, and ethnic diversity of the individuals in those cohorts. However, we note that
397 calibration of the developed risk equations may be poor in populations that differ substantially in the
398 adjusted incidence of reduced eGFR or in which ascertainment of reduced eGFR is more or less sensitive.
399
400 **Limitations**
401 This study has several limitations. First, the absence of albuminuria data in most nondiabetic cohorts
402 included in this study required that a statistical patch derived from nondiabetic cohorts with
403 albuminuria data be applied to the remaining cohorts in order to estimate how inclusion of albuminuria
404 altered the models. This approach allows valid estimation of risk even in the absence of albuminuria,
405 although clinical assessment of albuminuria improved risk estimation and detection of early stage CKD
406 defined by elevated albuminuria (A-stages) in the absence of reduced kidney function (G stages 1-2).[25]
407 Second, the risk equations developed in this study incorporated routinely collected demographic,
408 clinical, and laboratory data and their predictive accuracy might be enhanced by incorporating other
409 variables, including genotype data or newly identified biomarkers of early CKD.[26] Third, the risk
410 prediction equations developed in this study were intended to identify persons at increased risk of an
411 intermediate health outcome. The risks of progression from CKD to kidney failure, cardiovascular
412 disease, or death were not assessed by these equations. Fourth, no minimum change in eGFR was
413 required in the primary predictive model to become a case of CKD, so someone with a baseline eGFR of
414 61 ml/min/1.73m^2 and a follow-up eGFR of 59 ml/min/1.73m^2 would be considered to have the
415 outcome of interest. Fifth, calibration varied across setting, with particularly poor performance in some
416 of the research cohorts. The models for eGFR <45 and eGFR<30 ml/min/1.73 m^2 were poorly calibrated

in many of the development cohorts, which may be due in part to the low number of events and relatively short follow-up time.

Conclusions

Equations for predicting risk of incident chronic kidney disease were developed in over 5 million people from 34 multinational cohorts and demonstrated high discrimination and variable calibration in diverse populations.

Contributors: MEG and JC 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. RGN, JC, RG, MEG, KM, MW, and VS were responsible for the study concept and design. JC, SHB, YS, MEG, and KM 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. RGN, JC, MEG, and VS drafted the manuscript. MEG guarantees 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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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations

that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: CKD-PC has agreed with collaborating cohorts not to share data outside the consortium. Each participating cohort has its own policy for data sharing.

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Table 1. Baseline characteristics of the participants in the 31 nondiabetic and 15 diabetic cohorts.

Study	Country	N	Age	Female	eGFR (ml/min/1.73m^2)	History of CVD	Hypertension	Smoking	BMI
Nondiabetic cohorts									
ARIC	USA	12757	54 (6)	7082 (56%)	103 (14)	980 (8%)	4437 (35%)	7367 (58%)	27 (5)
AusDiab	Australia	6281	50 (12)	3471 (55%)	88 (14)	306 (5%)	1580 (25%)	2528 (41%)	27 (5)
Beijing	China	948	59 (9)	496 (52%)	85 (12)	127 (13%)	363 (38%)	321 (34%)	25 (3)
CARE	Canada	2923	57 (9)	343 (12%)	80 (13)	2923 (100%)	2432 (83%)	2332 (80%)	28 (7)
CHS	USA	2170	73 (4)	1341 (62%)	77 (11)	409 (19%)	1280 (59%)	1122 (53%)	27 (5)
CIRCS	Japan	10022	54 (9)	6275 (63%)	90 (14)	97 (1%)	3353 (33%)	3507 (35%)	23 (3)
ESTHER	Germany	3394	61 (6)	1885 (56%)	92 (15)	458 (13%)	2213 (65%)	1548 (47%)	27 (4)
Framingham	USA	2353	58 (9)	1290 (55%)	91 (16)	180 (8%)	828 (35%)	368 (16%)	28 (5)
Geisinger	USA	229448	50 (16)	132677 (58%)	95 (18)	23403 (10%)	113953 (50%)	110640 (49%)	30 (7)
GLOMMS 2	UK	24321	61 (14)	13598 (56%)	81 (15)	1962 (8%)	910 (4%)	NA	NA
Gubbio	Italy	1249	54 (6)	714 (57%)	85 (11)	44 (4%)	443 (35%)	688 (55%)	28 (4)
HUNT	Norway	34430	46 (13)	19114 (56%)	102 (15)	1170 (3%)	12377 (36%)	17992 (53%)	26 (4)
IPHS	Japan	70557	60 (10)	47934 (68%)	86 (12)	3603 (5%)	33626 (48%)	19565 (28%)	23 (3)
JHS	USA	2164	48 (11)	1312 (61%)	102 (17)	94 (4%)	885 (41%)	596 (28%)	31 (7)
JSHC	China	461797	63 (8)	279934 (61%)	94 (11)	34567 (9%)	193996 (42%)	62947 (14%)	23 (3)
Maccabi	Israel	939309	43 (15)	546440 (58%)	104 (17)	55138 (6%)	213398 (23%)	231695 (25%)	27 (5)
MESA	USA	4954	61 (10)	2623 (53%)	86 (13)	1 (0%)	2051 (41%)	2600 (53%)	28 (5)
Mt Sinai BioMe	USA	14590	48 (14)	8998 (62%)	93 (19)	722 (5%)	6385 (44%)	3910 (28%)	29 (7)
Ohasama	Japan	2346	60 (10)	1483 (63%)	98 (11)	91 (4%)	832 (35%)	349 (19%)	24 (3)
Okinawa8393	Japan	1624	50 (10)	957 (59%)	100 (13)	0 (0%)	NA	NA	24 (3)
Pima	USA	2733	28 (11)	1626 (59%)	125 (13)	NA	272 (10%)	793 (47%)	33 (8)
PREVEND	Netherlands	5977	49 (12)	3057 (51%)	97 (14)	247 (4%)	1773 (30%)	4160 (70%)	26 (4)

Rancho Bernardo	USA	639	64 (10)	369 (58%)	75 (11)	49 (8%)	232 (36%)	354 (56%)	26 (4)
RCAV	USA	1765629	59 (13)	133822 (8%)	85 (15)	256353 (15%)	1196576 (68%)	NA	29 (6)
RSIII	Netherlands	2292	56 (6)	1333 (58%)	87 (12)	126 (5%)	1375 (60%)	1572 (69%)	27 (4)
SCREAM	Sweden	716952	52 (17)	392827 (55%)	95 (17)	40554 (6%)	177249 (25%)	NA	NA
SEED	Singapore	2358	54 (9)	1246 (53%)	88 (14)	156 (7%)	1164 (50%)	700 (30%)	26 (4)
Taiwan MJ	Taiwan	101216	41 (12)	52658 (52%)	91 (15)	2474 (2%)	16560 (16%)	26037 (28%)	23 (3)
TLGS	Iran	8502	37 (13)	4753 (56%)	81 (13)	171 (2%)	1404 (17%)	1839 (22%)	26 (5)
Tromso	Norway	6007	58 (10)	3522 (59%)	95 (12)	283 (5%)	3183 (53%)	3877 (65%)	26 (4)
ULSAM	Sweden	1142	50 (1)	0 (0%)	98 (10)	5 (0%)	416 (36%)	NA	25 (3)
		4441084	54 (16)	1673180 (38%)	93 (17)	426693 (10%)	1996070 (45%)	509588 (26%)	27 (6)
Diabetic cohorts									
ADVANCE	Multiple*	9339	66 (6)	3774 (40%)	83 (13)	2235 (24%)	8003 (86%)	4024 (43%)	28 (5)
AusDiab	Australia	427	59 (11)	189 (44%)	84 (13)	70 (16%)	287 (67%)	205 (48%)	30 (6)
Beijing	China	343	62 (9)	168 (49%)	85 (12)	80 (23%)	184 (54%)	127 (37%)	25 (4)
Geisinger	USA	34463	58 (15)	16842 (49%)	93 (18)	8606 (25%)	27251 (79%)	17563 (52%)	34 (8)
HUNT	Norway	1564	54 (12)	709 (45%)	95 (14)	130 (8%)	932 (60%)	892 (57%)	28 (5)
JHS	USA	390	54 (10)	241 (62%)	101 (18)	46 (12%)	310 (79%)	131 (34%)	35 (8)
Maccabi	Israel	72480	60 (13)	32972 (45%)	92 (15)	18147 (25%)	54586 (75%)	21733 (30%)	31 (6)
MESA	USA	659	63 (9)	304 (46%)	90 (15)	0 (0%)	455 (69%)	343 (52%)	31 (6)
Mt Sinai BioMe	USA	2652	54 (13)	1598 (60%)	91 (19)	511 (19%)	2013 (76%)	923 (37%)	32 (8)
NZDCS	New Zealand	14819	58 (13)	7152 (48%)	86 (16)	2260 (15%)	10197 (82%)	6469 (44%)	32 (7)
Pima	USA	933	43 (14)	577 (62%)	114 (17)	NA	335 (36%)	291 (40%)	34 (8)
RCAV	USA	607132	63 (10)	20241 (3%)	83 (15)	157611 (26%)	551356 (91%)	NA	32 (6)
SCREAM	Sweden	34307	60 (16)	14224 (41%)	91 (17)	8041 (23%)	20408 (59%)	NA	NA
SEED	Singapore	1029	58 (9)	508 (49%)	88 (15)	151 (15%)	742 (72%)	311 (30%)	28 (5)

ZODIAC	Netherlands	1090	63 (11)	522 (48%)	77 (12)	310 (28%)	794 (73%)	249 (23%)	29 (5)
		781627	62 (11)	100021 (13%)	85 (15)	198198 (25%)	677853 (87%)	53261 (38%)	32 (6)

Values are mean (SD) or percent of total N. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; NA, not available. Racial distributions of the cohorts are available in **eTable 4** and the citations for each study are available in **eAppendix 2**.

* Participants are from Australia, Canada, China, Czech Republic, Estonia, France, Germany, Hungary, India, Ireland, Italy, Lithuania, Malaysia, Netherlands, New Zealand, Philippines, Poland, Russia, Slovakia, and United Kingdom.

Table 2. Weighted-average sub-hazard ratios of major risk factors for incident eGFR<60 ml/min/1.73m^2 in the nondiabetic and diabetic cohorts.

	Sub-Hazard Ratios (95% CI) for Incident eGFR<60ml/min/1.73m^2	
Risk factors	Non-diabetic model	Diabetic model
Age, per 5y	1.29 (1.27, 1.32)	1.14 (1.13, 1.15)
Female	1.20 (1.18, 1.22)	1.15 (1.11, 1.18)
Black	1.20 (1.13, 1.27)	1.10 (1.02, 1.18)
eGFR 60-90, per -5 ml	1.58 (1.57, 1.59)	1.43 (1.41, 1.44)
eGFR 90+, per -5 ml	1.37 (1.34, 1.41)	1.16 (1.14, 1.19)
History of CVD	1.22 (1.18, 1.26)	1.21 (1.17, 1.24)
Ever smoker	1.13 (1.10, 1.16)	1.00 (0.96, 1.04)
Hypertension	1.43 (1.40, 1.46)	1.44 (1.39, 1.50)
BMI, per 5 kg/m^2	1.07 (1.05, 1.08)	1.05 (1.04, 1.07)
ACR, per 10-fold increase	1.42 (1.37, 1.48)†	1.45 (1.42, 1.49)
HbA1c (for oral DM meds), per 1%		1.06 (1.05, 1.07)
Insulin vs. oral DM meds (at 7% hba1c)		1.11 (1.05, 1.19)
No meds vs. oral DM meds (at 7% hba1c)		0.86 (0.83, 0.89)
Interaction: HbA1c * insulin vs. oral DM meds, per 1%		1.02 (1.00, 1.05)
Interaction: HbA1c * No meds vs. oral DM meds, per 1%		1.04 (1.02, 1.06)
ACR missing indicator (set ACR=10)		0.96 (0.93, 1.00)

†ACR was modeled using a patch in the non-diabetes model in which the coefficient for ACR was estimated in the population with available ACR with the other coefficients fixed. The model allows for prediction when ACR is missing.

eTables 9 and **10** provide absolute risk and risk difference scenarios.

Abbreviations: ACR, urine albumin-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c.

Figure 1. Variation in baseline adjusted competing risk of incident eGFR<60 ml/min/1.73m^2 in nondiabetic (A and C) and diabetic (B and D) cohorts with frequent measures of serum creatinine concentration. All events (confirmed and unconfirmed) are shown in Panels A and B and confirmed events are shown in Panels C and D.

Numbers after the cohort name in the key indicate the mean follow-up time in years. Each line represents the adjusted baseline risk in an individual cohort. The risk was determined by holding the weighted-average coefficients constant and fitting a multivariable competing risk model in each study. The adjusted sub-hazard was smoothed using a Weibull distribution. The pooled line represents the weighted mean which is used in the prediction equation.

Figure 2. Predicted 5-year absolute risk of incident eGFR <60 ml/min/1.73m^2 is shown for various scenarios in three ages and albuminuria categories in nondiabetic and diabetic individuals. All 5-year risks were computed for hypothetical individuals with a baseline eGFR of 90 ml/min/1.73m^2. For the 5-year predicted risk in a hypothetical individual with diabetes, the hemoglobin A1c was also set to 7.7% and the individual was assumed to be receiving an oral diabetes medicine. Scenarios: Sex: male/female, Ethnicity: non-black/black, History of CVD: yes/no, Smoker: yes/no, Hypertension: yes/no, BMI: 25/35 kg/m^2, ACR: not available (N/A; equation without ACR)/50/500 mg/g (non-DM); 5/50/500 mg/g (DM). Abbreviations: ACR, urine albumin-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus.

*Each column contains 64 dots representing 64 hypothetical scenarios. The dots are shaded from light to dark based on the number of risk factors present, scaled from 0 to 4 based on the presence or absence of CVD, smoking, hypertension, and BMI 35 kg/m^2.