Original Article

Prediction models and nomograms of 3-year risk of chronic kidney disease in China: a study from the Shanghai Suburban Adult Cohort and Biobank (2016–2020)

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Background: Chronic kidney disease (CKD) is a serious public health problem in China that requires the development and verification of sex-specific 3-year risk prediction models and nomograms of CKD to further guide personalized care.

Methods: A 3-year community-based observational cohort study of 10,049 Chinese participants without CKD was begun in 2016 and participants were followed until August 2020. Stepwise multivariable-adjusted Cox regression analyses were conducted to select the candidate variables, including demographics and clinical parameters such as blood urea nitrogen (BUN) and estimated glomerular filtration rate (eGFR), into the prediction model. We used the C-statistic to evaluate discrimination, and the Brier score for calibration. A 10-fold cross-validation was conducted for internal validation to assess the model's stability.

Results: The cumulative incidence of CKD was 4.25% (male: 3.81%, female: 4.55%). The eGFR, HbA1c variability, uric acid (UA), UA variability, BUN, albumin, and Hb were significant predictors for both sexes. In the female model, age, triglycerides and age at menarche were additional predictors. The models showed C-statistics of 0.934/0.951 (male/female). The model calibrated well across the deciles of predicted risk, with a Brier score of 0.007/0.009 (male/female).

Conclusions: In this study, we fitted the CKD 3-year risk prediction models with an accuracy rate of >90%. At the same time, we developed two nomograms to facilitate routine CKD risk prediction to provide individualized care in preventing or delaying CKD.

Keywords: Chronic kidney disease (CKD); nomograms; risk prediction models

Submitted Sep 29, 2021. Accepted for publication Nov 16, 2021.
doi: 10.21037/atm-21-5647
View this article at: https://dx.doi.org/10.21037/atm-21-5647

Introduction

Chronic kidney disease (CKD) is a progressive and lifelong disease in public health. CKD is characterized by abnormal renal structure or function, including glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, abnormal renal structure detected as proteinuria or by imaging, and symptoms lasting >3 months (1). There were 752.7 million CKD patients worldwide in 2016, and 55% of the patients were women (2,3). CKD complications contain cardiovascular disease (CVD), hypertension, anemia, bone disease, electrolyte abnormalities, and in the end stages uremia. CKD is a risk

factor for death. The risk factors of CKD are: age (such as old age), CKD family history (including hereditary and non-hereditary nephropathy), diabetes mellitus, hypertension, etc.

Prevention of CKD is an important goal of health management. An accurate CKD risk prediction model can effectively identify high-risk individuals. There are several existing prediction models, but most were developed from Western populations. Studies have showed that Chinese people are more likely to develop CKD than Caucasian people due to environmental (i.e., diet and lifestyle) and genetic factors. In addition, the existing prediction models of CKD are primarily based on established risk factors such as age, body mass index (BMI), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) (2-7). Previous studies have showed that there were sex-related disparities in CKD incidence and progression (5,8,9), and there are differential effects of some clinical and lifestyle factors on the incidence of chronic diseases such as CKD or diabetes mellitus (DM) in males and females (10,11). Women also have some reproductive factors such as age at menarche (12) and times of pregnancy (number of times the woman was pregnant) that are independent variables in CKD (13,14). Women benefit from estrogen, probably acting on the renin-angiotensin-aldosterone system before menopause, after which their risk of CVD and osteoporosis increases, and most women with CKD are postmenopausal (15,16). However, there are few studies of sex-specific CKD prediction models, especially containing female reproductive factors (2,4,9).

Therefore, this study aimed to develop and internally validate sex-specific 3-year risk prediction models of CKD. The objectives were to: (I) develop CKD risk prediction models, (II) internally validate the developed models, and (III) develop nomograms for clinical application. This research is a modelling analysis of chronic kidney disease conducted in Shanghai, which is an update and supplement for this direction. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5647).

Methods

Study design

The data in this study was obtained from the Shanghai Suburban Adult Cohort and Biobank (SSACB) (13), which is a community-based cohort study conducted by the School of Public Health of Fudan University and Shanghai Songjiang Center for Disease Control and Prevention from June 2016 to August 2020. SSACB sampled a representative sample of seven communities in the rapidly urbanizing suburbs, Songjiang, and Jiading, and linked them to the local population-based information system. The first follow-up of SSACB was conducted from June 2019 to August 2020, and the baseline assessment was conducted from June 2016 to December 2017. This study conducted a multi-stage stratified cluster sampling method to recruit study participants. The inclusion criteria are (I) Shanghai natives or have lived in Shanghai for at least 5 years, (II) age between 20–74 years old, and. The exclusion criteria were (I) unable to agree, (II) history of CKD, (III) pregnancy, (IV) serious diseases such as cancer, stroke, cirrhosis, cardiopulmonary failure, and hyperthyroidism or hypothyroidism. In this study, 10,891 individuals without CKD at baseline were included. After excluding individuals with incomplete data (physical examination, questionnaire survey, or laboratory measurement), 10,049 qualified subjects were finally included. The study was approved by the Ethical Review Committee of School of Public Health, Fudan University (IRB approval No. 2016-04-0586). All participants signed a written informed consent form. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Exposure assessment

As the baseline, data on date of birth, smoking status, alcohol consumption, self-reported medical history of chronic diseases, age at menarche and pregnancies were collected using a structured questionnaire administered by trained interviewers. Smoking status was defined as smoking >1 cigarette/day for 6 months. Alcohol intake was defined as drinking >3 times per week for at least 6 months. In this study, the diagnosis of type 2 diabetes (T2DM) was based on the International Diabetes Federation fasting plasma glucose (FPG) standard ≥7.0 mmol/L or hemoglobin Alc (HbA1c) ≥6.5% or the previous diagnosis of T2DM (17). Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg and/or a previous diagnosis of hypertension. Measure height and weight in duplicate according to a standardized protocol, and determine the average value. The definition of BMI (kg/m^2) in the baseline data was weight (kg) divided by the square of height (m). Menopause was defined as a retrospective diagnosis of menstrual cessation for more than 12 months. Procedures

for blood sampling and analytic methods were as previously described (18-20).

Outcome

CKD was defined as ICD-10 in the medical records, or eGFR <60 mL/min/1.73 m^2, according to the National Kidney Foundation Classification, or as the albumin/creatinine ratio (ACR) >30. The eGFR was calculated to estimate kidney function using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for the Chinese population.

Potential predictors

Variables that were considered clinically relevant or showed a univariate relationship with outcome were included as possible predictors. They were categorized as demographic (age, family history of CKD, alcohol intake, smoking status), disease history (hypertension, DM), baseline clinical parameters [BMI, Hb, HbA1c, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), eGFR, uric acid (UA), blood urea nitrogen (BUN), albumin (ALB)], and for the female-specific model, we included reproductive factors (age at menarche, length of reproductive period, pregnancy times (number of times the woman was pregnant.), menopause). Studies have showed that variability of SBP, UA, HbA1c (21,22) is associated with CKD independent of SBP, UA, HbA1c. In this study, we included these parameters in the model, which were measured by the standard deviation (SD) of SBP and HbA1c, respectively.

Model development and validation

In this study, we stepwise applied Cox proportional hazard regression to establish the risk prediction model. At the same time, the proportional hazard hypothesis was tested by examining the relationship between the scaled Schoenfeld residuals of the covariates and time. Prediction models were developed for each sex. The nomogram included the hazard ratios, which were converted from the regression coefficient for each covariate. The Harrell C-statistic and Brier score were estimated to evaluate model discrimination and calibration. The C-statistic indicates the consistency between the predicted and actual results. The Brier score comprehends both calibration and discrimination, which is the mean squared difference between the observed and predicted outcomes. Furthermore, 10-fold cross-validation was conducted to validate the stability of the model, considering there was no external validation in the present study.

To compare the newly developed models with existing models, a comparison was conducted with a published equation identified in a review (2). Chien *et al.* developed their equation using 5,168 Chinese participants and the median follow-up of the study was 2.2 years (23). In our study, we included age, BMI, history of T2DM and stroke, and DBP as potential predicators, which were used in the Chien clinical equation. In addition, the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were used to evaluate the added predictive ability of the new developed models. Larger values of NRI and IDI show greater improvements in model discrimination.

Statistical analysis

The data were analyzed using Stata 16.0 (StataCorp, Dallas, TX, USA) and R (Version 4.0.3). The pmsampsize package of Stata was used to calculated the minimum sample size for the study (24), considering the mean follow-up of 36 months, 18/22 (male/female) candidate predictors and the CKD incidence, and the minimum sample for each sex to develop the prediction models was 3,150 for men and 3,849 for women.

Student's *t*-test and the Wilcoxon-Mann-Whitney test were used for normal and non-normal parameters, respectively. The Pearson chi-square test was used for categorical data presented as n (%). P values <0.05 were considered statistically significant. The Cox proportional hazards model with backward stepwise method was used to develop the risk prediction models. The nomograms were generated using Cox regression coefficients in R software.

Results

Baseline characteristics of the participants

A total of 10,049 participants were included in this study: 4,117 (41.0%) were male and 5,932 (59.0%) were female. The mean age was 57.1 years (male: 58.1; female: 56.4). *Table 1* summarizes the baseline characteristics, including all potential predictors, grouped by sex. During a median follow-up period of 36 months, 427 subjects (male: 157, female: 270) developed CKD. The 3-year cumulative incidence of CKD was 4.25% (male: 3.81%, female: 4.55%). The incidence of CKD was higher in females than in males.

Table 1 Baseline characteristics of subjects

Characteristics	Total cohort (N=10,049)	Male			Female		
		Without CKD (N=3960)	With CKD (N=157)	P value	Without CKD (N=5662)	With CKD (N=270)	P value
Age (years)	57.1 (10.0)	58.0 (10.2)	60.6 (9.9)	<0.001	56.2 (9.8)	61.5 (9.0)	<0.001
Smoking	2,367 (23.6)	2,271 (57.3)	86 (54.8)	0.52	10 (0.2)	0 (0.0)	0.49
Alcohol intake	1,447 (14.4)	1,347 (34.0)	56 (35.7)	0.67	43 (0.8)	1 (0.4)	0.47
Family history of CKD	72 (0.7)	11 (0.3)	2 (1.3)	0.029	57 (1.0)	2 (0.7)	0.67
Clinical parameters							
BMI (kg/m^2)	24.5 (3.3)	24.7 (3.1)	25.9 (3.5)	<0.001	24.3 (3.4)	25.1 (3.2)	<0.001
T2DM	1,522 (15.1)	597 (15.1)	45 (28.7)	<0.001	812 (14.3)	68 (25.2)	<0.001
HbA1c SD (%)	0.3 (0.4)	0.3 (0.4)	0.4 (0.6)	<0.001	0.2 (0.3)	0.3 (0.5)	0.012
Hypertension	5,532 (55.1)	2277 (57.5)	118 (75.2)	<0.001	2,948 (52.1)	189 (70.0)	<0.001
SBP SD (mmHg)	9.9 (8.4)	9.8 (8.2)	12.2 (11.3)	0.031	9.8 (8.3)	10.5 (9.4)	0.034
BUN (mg/dL)	14.8 (3.7)	14.9 (3.7)	16.4 (4.6)	<0.001	14.6 (3.6)	16.1 (4.1)	<0.001
HDL-C (mg/dL)	54.0 (13.2)	49.7 (11.5)	47.3 (11.1)	0.019	57.1 (13.5)	54.1 (13.2)	<0.001
TG (mg/dL)	145.8 (105.8)	151.6 (120.6)	180.1 (145.4)	<0.001	139.7 (91.0)	170.6 (123.4)	<0.001
ALB (g/dL)	4.9 (0.3)	4.9 (0.3)	5.0 (0.3)	0.357	4.9 (0.3)	4.9 (0.3)	0.697
Hb (g/dL)	14.1 (1.4)	15.3 (1.1)	15.0 (1.2)	0.010	13.4 (1.0)	13.2 (1.2)	0.015
UA (mg/dL)	5.1 (1.3)	5.9 (1.3)	6.4 (1.5)	<0.001	4.6 (1.1)	5.3 (1.4)	<0.001
UA SD (mg/dL)	0.5 (0.5)	0.6 (0.5)	0.9 (0.8)	<0.001	0.5 (0.4)	0.7 (0.6)	<0.001
eGFR (mg/dL)	92.4 (12.9)	90.8 (12.2)	80.1 (16.1)	<0.001	94.2 (12.6)	82.9 (16.0)	<0.001
Age at menarche							<0.001
<17 years	3,934 (66.3)	–	–	–	3,795 (67.0)	139 (51.5)	–
≥17 years	1,998 (33.7)	–	–	–	1,867 (33.0)	131 (48.5)	–

Data were expressed as mean (SD) or n (%). BMI, body mass index; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; BUN, blood urea nitrogen; HbA1c, glycated hemoglobin; SD, standard deviation; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Hb, hemoglobin; ALB, albumin; UA, uric acid; eGFR, estimated glomerular filtration rate.

Compared with subjects who did not develop CKD, those who developed CKD were older and had a higher metabolic risk profile, including higher BMI, BUN, TG, variability in HbA1c, SBP, and UA, and lower levels of HDL-C and Hb in both male and female subjects. Among females, the proportion of older age at menarche (≥17 years) was higher in subjects who developed CKD (*Table 1*).

Development of risk prediction models

Sex-specific CKD risk prediction models were developed by Cox regression. *Table 2* and *Table 3* showed the Cox regression models for females and males, respectively. eGFR, HbAlc variability, UA, UA variability, BUN, ALB, and Hb were statistically significant predicators in both males and females. Additional significant predictors for females were age, TG and age at menarche. The sex-specific nomograms were developed from the hazard ratios converted by the coefficients for each predictor to predict the 3-year risk of CKD (*Figure 1*). The C-statistics of the sex-specific prediction models were 0.934 [95% confidence interval (CI): 0.901–0.968] and 0.951 (95% CI: 0.930–0.972) for male and female, respectively. The calibration plots showed good agreement between predicted and observed outcomes for the sex-specific CKD prediction models, with a Brier score of 0.007/0.009 for male/female (*Figure 2*). The

Table 2 Three-year CKD risk prediction models for males using Cox regression analysis

Risk factors	HR (95% CI)	P value
eGFR (mg/dL)	0.95 (0.93–0.96)	<0.001
HbA1C SD (%)	2.13 (1.65–2.76)	<0.001
UA (mg/dL)	1.15 (1.02–1.29)	0.019
UA SD (mg/dL)	1.46 (1.24–1.72)	<0.001
BUN (mg/dL)	1.05 (1.01–1.10)	0.007
ALB (g/dL)	0.64 (0.36–1.12)	0.115
Hb (g/dL)	0.85 (0.75–0.97)	0.015

Data are expressed as HR (95% CI). The HR, 95% CI, and P values were analyzed using Cox regression analysis. CKD, chronic kidney disease; BUN, blood urea nitrogen; HbA1c, glycated hemoglobin; SD, standard deviation; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Hb, hemoglobin; ALB, albumin; UA, uric acid; eGFR, estimated glomerular filtration rate; HR, hazard ratios; CI, confidence interval.

Table 3 Three-year CKD risk prediction models for females using Cox regression analysis

Risk factors	HR (95% CI)	P value
Age (years)	1.02 (1.00–1.04)	0.018
eGFR (mg/dL)	0.95 (0.94–0.96)	<0.001
TG (mg/dL)	1.00 (1.00–1.00)	0.002
HbA1C SD (%)	1.68 (1.35–2.09)	<0.001
UA (mg/dL)	1.28 (1.15–1.42)	<0.001
UA SD (mg/dL)	1.38 (1.13–1.69)	0.002
BUN (mg/dL)	1.05 (1.01–1.08)	0.006
ALB (g/dL)	0.44 (0.28–0.69)	<0.001
Hb (g/dL)	0.88 (0.79–0.97)	0.009
Age at menarche (years)		
<17	–	–
≥17	1.24 (0.95–1.61)	0.108

Data are expressed as HR (95% CI). The HR, 95% CI, and P values were analyzed using Cox regression analysis. CKD, chronic kidney disease; BUN, blood urea nitrogen; HbA1c, glycated hemoglobin; SD, standard deviation; TG, triglycerides; Hb, hemoglobin; ALB, albumin; UA, uric acid; eGFR, estimated glomerular filtration rate; HR, hazard ratios; CI, confidence interval.

nomograms are presented in *Figure 3*.

Validation of risk prediction models

A 10-fold cross-validation was used to validate the reliability of our models. The mean of the C-statistics was 0.918 and 0.958 for male and female, respectively. The mean of the Brier score were 0.007 and 0.009 for male and female, respectively. The 10-fold validation method showed perfect stability of the models' predictive power.

Comparison with existing equation

The newly developed sex-specific models for CKD had better discrimination than the Chien model. The difference in C-statistics was 0.120 (P value <0.001) and 0.059 (P value <0.001) for male and female, respectively. Compared with the Chien model, significantly higher NRIs and IDI were observed for the newly developed sex-specific models. The NRIs were 0.615 (95% CI: 0.485–0.712, P value <0.001) and 0.530 (95% CI: 0.399–0.643, P value <0.001) for male and female, respectively, and the IDIs were 0.027 (95% CI: 0.015–0.054, P value <0.001) and 0.045 (95% CI: 0.027–0.071, P value <0.001).

Discussion

To the best of our knowledge, this is the first risk prediction model to consider women's reproductive factors (age at menarche, menopause and times of pregnancy) as potential predicators that have been found to have independent associations with incident CKD in the previous literature (16,25). In our study, age at menarche was a strong predictor of incident CKD.

In this study, we developed and validated internally our sex-specific risk prediction models and nomograms for CKD, aiming at providing simple and efficient tools for tailored CKD screening by effectively identifying high-risk subpopulations. Using SSACB's data (median 36 months) of a community-based cohort, the sex-specific prediction models we developed were superior to an existing CKD risk prediction model, showing outstanding performance with means of the C-statistic of 0.918 and 0.958 for male and female, respectively. A total of 7 predicators (eGFR, HbA1c variability, UA, UA variability, BUN, ALB, Hb) were included in both models. In the female model, age, TG and age at menarche were additional predictors. Self-validation and 10-fold cross validation verified the reliability and accuracy of our model with excellent C-statistics and Brier scores.

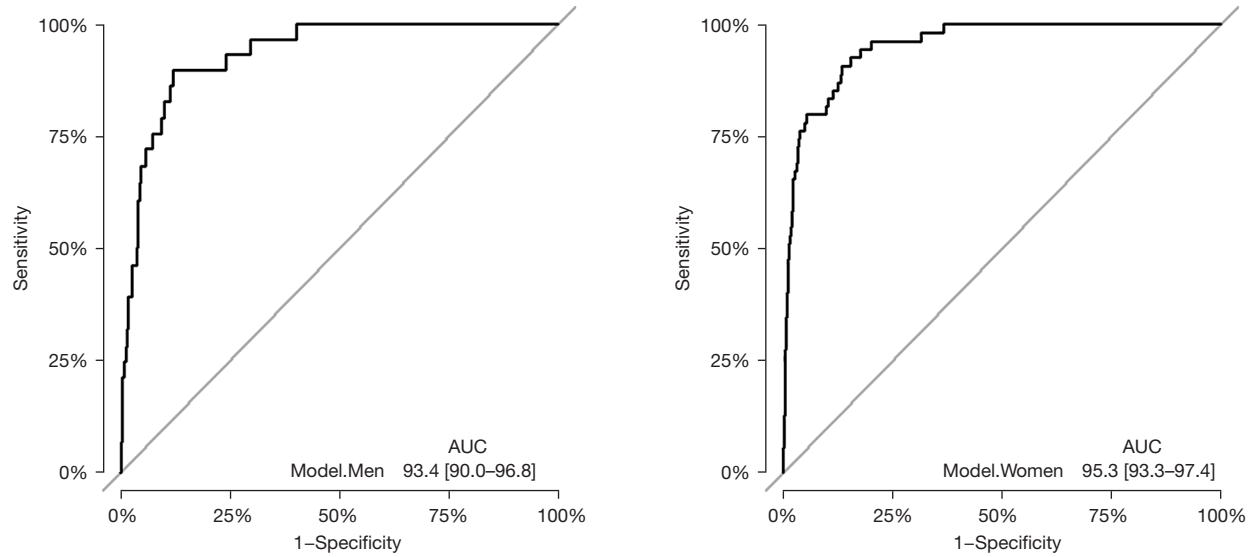

Figure 1 ROC curves of CKD risk prediction in 3 years for men and women. AUC, area under the curve; ROC, receiver-operating characteristic; CKD, chronic kidney disease.

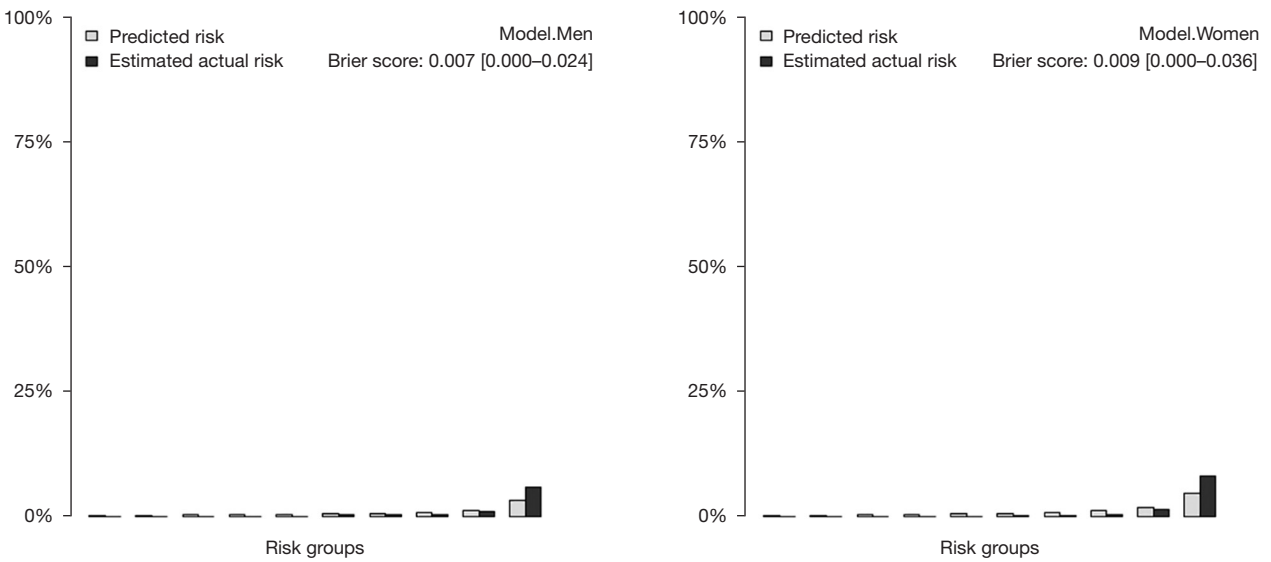

Figure 2 Calibration plots for men and women. The x-axis represents the model-predict incident CKD risk and the y-axis represents actual incident CKD risk. CKD, chronic kidney disease.

A cornerstone of personalized and individualized medicine is improved clinical prediction, and the Framingham cardiovascular risk score is a famous example that has helped shape public health policy in the primary prevention of CVD (26). However, similar well-known models for kidney disease do not exist, despite the identification of several key renal risk factors by previous studies. In our study, during the follow-up period of 3 years, CKD incidence was 4.25%, and was higher in females (4.55%) than in males (3.81%). This CKD incidence is comparable with other Chinese cohorts (23) but higher than in Western populations (4). Studies have showed that the incidence of end-stage renal disease is 1.5-fold higher in men than in women, despite men's prevalence of CKD

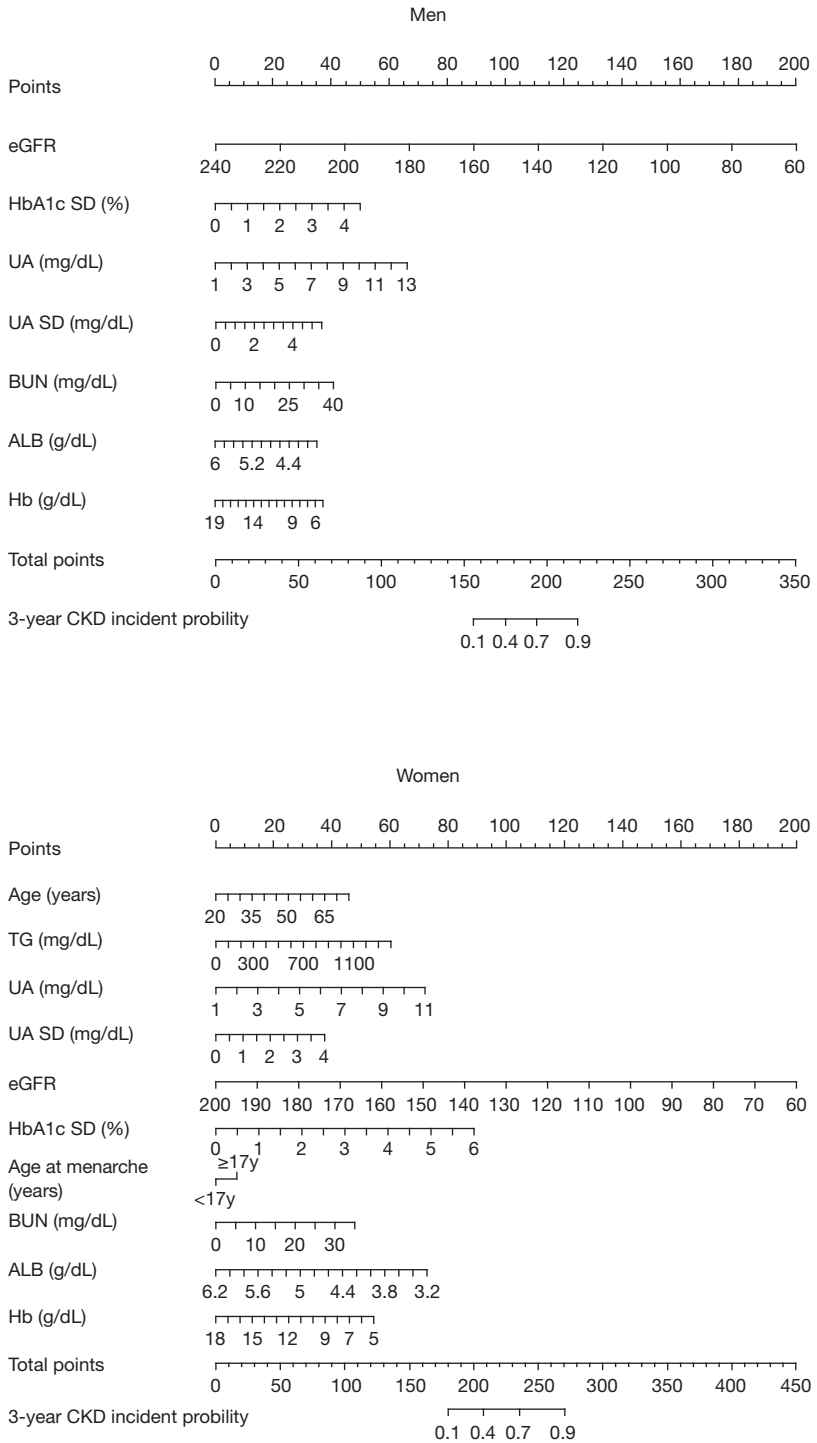

Figure 3 Nomograms for predicting the risk of CKD in 3 years for men and women. Steps to estimate the risk of CKD in 3 years: (I) by drawing a vertical line from the parameter value to the scoring ruler, the score of each parameter is obtained; (II) the total score is obtained by adding all the parameter scores; (III) a vertical line is drawn from the total score to the predicted 3-year risk scale. ALB, albumin; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; TG, triglycerides; UA, uric acid; CKD, chronic kidney disease.

being lower than that of women (8). Women have a higher incidence of CKD but lower risk of CKD progression and death compared with men. The sex-related disparity can be explained by the differential effects of sex on lifestyle and traditional risk factors such as BMI and laboratory parameters such as HbA1c, and UA (10,11) as well as the protective effect of endogenous testosterone and sex differences in nitric oxide metabolism. Various studies of the risk factors and prediction models of CKD have been published, but few are sex-specific and none include women's reproductive factors that are associated with the incidence of chronic diseases such as CKD, hypertension and DM (27-31). Given this, developing sex-specific risk prediction models of CKD is essential and could provide more precise decision-making support in sex-specific health management. In our women's model, we included age at menarche, times of pregnancy and postmenopausal status as potential predictors for incident CKD, and age at menarche was found to be a strong predictor for incident CKD. The mechanism may lie in late age at menarche, which is associated with higher BMI, waist circumference and higher risk of hypertension, and DM (31), thus increasing the risk of incident CKD. Further study should consider including more of women's reproductive characteristics as potential predictors for incident CKD and further validate the hypothesis that women's reproductive characteristics have predictive power to some extent.

In our study, most of our predictors were significantly associated with incident CKD, supporting the findings of previous studies and indicating our model's reliability. It is worth noting that variability of HbA1c and UA was found to be a significant predictor of CKD, which substantiated the finding by other studies of an association between them (21,32) and adds new significant predictors to the models. Previous study showed some possible explanations for the associations. The effects of high glucose on the kidney include increased glomerular permeability, expression of fibrinogenesis markers, circulating levels of inflammatory cytokines, mesangial and tubulointerstitial cell matrix production, and the generation of free radicals that induce diabetic complications (33-36). Either high or low levels of UA may be directly toxic to the kidney, and the level of UA has to be just right (32).

Our study has several advantages. First, all the predictors involved in the models are easily accessible from routine medical examinations. They are either demographic characteristics or basic clinical parameters, which means they are affordable even for clinical practice with poor medical resources. Second, the nomograms were generated in the study, which allowed visual tracking of the risk assessment. Nomograms are easy for clinicians and non-professionals to use without complex calculations. Thirdly, our model included variability of HbA1c and UA, which allows people to predict risk from multiple clinical measurements, not just a single one. Thus, the models developed may be especially useful for chronic disease patients such as diabetic patients. Finally, the data for eGFR were calculated based on the CKD-EPI equation instead of MDRD, which is consistent with international standards and other studies on this issue. In addition, the established model in the research is more accurate based on the big data than several previous models and it can play a role in the prevention and control of CKD.

However, our study also has a few limitations. First, given the women's reproductive characteristics were self-reported, there may be errors in recalling their menarche and menopause ages. Second, only internal validation was conducted to assess the model's performance. In further research, external validation is needed to strengthen our models' stability.

Conclusions

The 3-year CKD risk of the general population can be predicted with >90% accuracy using routinely accessible parameters. Sex-specific risk prediction models and nomograms have been developed and can be widely applied in health management without needing complex calculation, which can assist clinicians in preventing the onset or delaying the progression of CKD.

Acknowledgments

The authors are grateful for the invaluable participation of the subjects.
Funding: This work was supported by grants from the National Key Research and Development Program of China, Precision Medicine Project (Grant No. 2017YFC0907001), and the Shanghai New Three-year Action Plan for Public Health (Grant No. GWV-10.1-XK16).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.

org/10.21037/atm-21-5647

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-5647

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-5647). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Review Committee of School of Public Health, Fudan University (IRB approval No. 2016-04-0586). All participants signed a written informed consent form.

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Cite this article as: Yu Y, Zhao Q, Jiang Y, Wang N, Liu X, Qiu Y, Zhu J, Tong X, Cui S, Zhao G. Prediction models and nomograms of 3-year risk of chronic kidney disease in China: a study from the Shanghai Suburban Adult Cohort and Biobank (2016–2020). Ann Transl Med 2021;9(22):1690. doi: 10.21037/atm-21-5647

