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Revised Equations for Estimated GFR From Serum Creatinine in Japan

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Background: Estimation of glomerular filtration rate (GFR) is limited by differences in creatinine generation among ethnicities. Our previously reported GFR-estimating equations for Japanese had limitations because all participants had a GFR less than 90 mL/min/1.73 m^2 and serum creatinine was assayed in different laboratories.

Study Design: Diagnostic test study using a prospective cross-sectional design. New equations were developed in 413 participants and validated in 350 participants. All samples were assayed in a central laboratory.

Setting & Participants: Hospitalized Japanese patients in 80 medical centers. Patients had not participated in the previous study.

Reference Test: Measured GFR (mGFR) computed from inulin clearance.

Index Test: Estimated GFR (eGFR) by using the modified isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation using the previous Japanese Society of Nephrology Chronic Kidney Disease Initiative (JSN-CKDI) coefficient of 0.741 (equation 1), the previous JSN-CKDI equation (equation 2), and new equations derived in the development data set: modified MDRD Study using a new Japanese coefficient (equation 3), and a 3-variable Japanese equation (equation 4).

Measurements: Performance of equations was assessed by means of bias (eGFR − mGFR), accuracy (percentage of estimates within 15% or 30% of mGFR), root mean squared error, and correlation coefficient.

Results: In the development data set, the new Japanese coefficient was 0.808 (95% confidence interval, 0.728 to 0.829) for the IDMS–MDRD Study equation (equation 3), and the 3-variable Japanese equation (equation 4) was eGFR (mL/min/1.73 m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female). In the validation data set, bias was −1.3 ± 19.4 versus −5.9 ± 19.0 mL/min/1.73 m^2 ($P = 0.002$), and accuracy within 30% of mGFR was 73% versus 72% ($P = 0.6$) for equation 3 versus equation 1 and −2.1 ± 19.0 versus −7.9 ± 18.7 mL/min/1.73 m^2 ($P < 0.001$) and 75% versus 73% ($P = 0.06$) for equation 4 versus equation 2 ($P = 0.06$), respectively.

Limitation: Most study participants had chronic kidney disease, and some may have had changing GFRs.

Conclusion: The new Japanese coefficient for the modified IDMS–MDRD Study equation and the new Japanese equation are more accurate for the Japanese population than the previously reported equations.
Am J Kidney Dis 53:982-992.

INDEX WORDS: Glomerular filtration rate; Japanese; inulin clearance; serum creatinine.

Editorial, p. 932

Glomerular filtration rate (GFR) is the most accurate index for assessing overall kidney function and an important tool for making diagnostic decisions in clinical practice.[1] GFR may be measured by using the clearance of an exogenous marker; inulin is the gold standard, but the method is not applicable to daily practice because it is time consuming, labor intensive, and expensive. Kidney function usually is assessed from serum creatinine (SCr) concentration alone, but SCr is affected by creatinine generation, including muscle mass and dietary intake, in addition to GFR.[2] GFR can be estimated from SCr level by using equations that include age, sex, race, and serum urea nitrogen (SUN) and albumin levels, as surrogates for creatinine generation, and are more accurate than estimates based on SCr level alone.[1,3,4]

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A list of the investigators who helped develop the Japanese equation for estimated GFR appears at the end of the article.

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The Modification of Diet in Renal Disease (MDRD) Study equation[5] and Cockcroft-Gault (CG) equation[6] are most commonly used for GFR estimation worldwide. Recently, the 4-variable MDRD Study equation was reexpressed by Levey et al[7] for use with isotope dilution mass spectrometry (IDMS)-standardized SCr values (the IDMS–MDRD Study equation). Several studies have validated the MDRD Study equation in whites and blacks.[8-14] In studies of more than 5,500 participants, Stevens et al[15,16] reported that GFR estimates using the IDMS–MDRD Study equation were unbiased and accurate for interpretations of GFR less than 60 mL/min/1.73 m^2, but warned that estimates just less than 60 mL/min/1.73 m^2 must be interpreted with caution to prevent misclassification of chronic kidney disease. The equation is less accurate for Asians, with greater bias at estimated GFR (eGFR) less than 60 mL/min/1.73 m^2.[17-19] Accordingly, both Ma et al[17] and our investigators[18,19] modified the MDRD Study equation by using separate "correction coefficients" for Chinese and Japanese. In both studies, the new equations were more accurate than the MDRD Study equation, but the correction coefficients were considerably different, with a Chinese coefficient of 1.233[17] and Japanese coefficient of 0.741.[19]

The difference in correction coefficients between Japanese and Chinese has not been explained. In our previous study, there may have been nonuniformity of creatinine assays because study samples for SCr were assayed in multiple laboratories and during different periods. Furthermore, data from participants with GFR greater than 90 mL/min/1.73 m^2 were not used for deriving the equation in the study. To verify results of our previous study, a new project was launched by the Japanese Society of Nephrology (JSN) with cooperation of nephrologists nationwide. The new study was conducted in 763 individuals to measure GFR and SCr by using inulin clearance (Cin) and standardized assays. A new Japanese correction coefficient was derived, as were new 3- and 5-variable Japanese equations.

METHODS

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) age 18 years and older; (2) relatively stable kidney function, assessed by using SCr level; and (3) patient's agreement to have urinary Cin measured using a continuous infusion.

Exclusion criteria were: (1) acute kidney injury, (2) apparent malignancy, (3) problems in micturition, (4) pregnancy, (5) inulin allergy, (6) amputation, and (7) individuals for whom the investigator judged that measuring Cin was inappropriate. Although some study participants were hospitalized for diagnosis of rapidly progressive or acute glomerulonephritis, renal biopsies and Cin measurements were performed after their conditions became relatively stable. We did not record data for day-to-day SCr level changes.

Study Population of the Data Set

The study recruited participants from 80 medical centers throughout Japan between December 2006 and July 2007. Participants included mostly nephrology inpatients. Hospitalization of 5 to 14 days for kidney biopsy or education about lifestyle change was commonly practiced in Japan. Data for Cin and SCr were collected from 878 participants, mostly those with chronic kidney disease and a small number of healthy kidney donors. A total of 115 participants were excluded for the following reasons: 36 lacked data for urine volume, 11 were 17 years and younger, 2 had high serum inulin concentrations, 4 had lack of data for inulin blank, 51 had high values for inulin blank, 9 had a low volume of voided urine (<10 mL), and 2 had extraordinarily high GFRs. The final study population included 763 participants. Data collected from December 1, 2006, to April 20, 2007 (n = 413), were used as the development data set, and those obtained from April 21, 2007, to July 31, 2007 (n = 350), were used as the validation data set. The institutional review board at all the study institutions approved anonymous use of data for the present study. All patients signed written informed consent.

Cin and Creatinine Renal Clearance

Cin and creatinine clearance (Ccr) were measured simultaneously in 757 participants. In 6 participants, only Cin was measured. The method for measuring renal Cin was described elsewhere.[18] Briefly, Cin and Ccr were calculated from serum and urine concentrations and urine flow rate. Inulin (1%) was administered by means of a continuous intravenous infusion for 2 hours under overnight fasting, but hydrated, conditions. During the inulin infusion, serum samples were collected 4 times at 0 (blank), 45, 75, and 105 minutes for creatinine and inulin, and urine samples were collected between 30 and 60, 60 and 90, and 90 and 120 minutes for inulin and creatinine after completely emptying the bladder at 30 minutes from the start of the inulin infusion. Inulin samples were assayed by means of an enzymatic method using a kit (Diacolor Inulin; Toyobo Co, Osaka, Japan). The mean value of 3 measurements was used for the Cin and Ccr study.

SCr Measurement

Serum samples were assayed for creatinine in a central laboratory (Central Laboratory; SRL Co, Hachioji, Japan) by means of the enzymatic creatinine assay method using an

Table 1. Participant Characteristics

	Development Data Set	Validation Data Set
No. of participants (men/women)	413 (262/151)	350 (203/147)
Age (y)	51.4 ± 16.5 (18-88)	53.9 ± 17.5 (19-91)
Serum creatinine (mg/dL)	1.62 ± 1.59 (0.41-10.75)	1.57 ± 1.38 (0.34-10.28)
Albumin (g/dL)	3.80 ± 0.64 (1.70-5.20)	3.91 ± 0.56 (1.70-5.10)
Serum urea nitrogen (mg/dL)	22.0 ± 15.5 (5.0-107.3)	22.4 ± 14.2 (6.1-81.2)
GFR (mL/min/1.73 m^2)	59.1 ± 35.4 (3.0-199.3)	57.2 ± 34.7 (2.6-228.7)
0-29	108 (26%)	93 (27%)
30-59	115 (28%)	113 (32%)
60-89	102 (25%)	73 (21%)
>90	88 (21%)	71 (20%)
Creatinine clearance (mL/min/1.73 m^2)	81.2 ± 47.2 (3.1-274.1)	79.7 ± 44.9 (5.3-268.5)
Height (cm)	163.3 ± 8.8	161.6 ± 9.5
Weight (kg)	61.0 ± 12.9	60.4 ± 12.7
Body surface area (m^2)	1.65 ± 0.19	1.63 ± 0.19
Diagnosis		
Chronic glomerulonephritis	219	173
Acute glomerulonephritis	4	3
RPGN	10	4
Interstitial nephritis	6	3
Diabetes mellitus	46	44
Polycystic kidney disease	2	0
Nephrosclerosis	25	30
Lupus	10	3
Kidney donor	1	10
Kidney recipient	9	2
Hereditary nephritis	3	1
Hypoplasia	3	0
Unilateral nephrectomy	6	3
Miscellaneous	69	74

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; urinary albumin in g/dL to g/L, ×10; serum urea nitrogen in mg/dL to mmol/L, ×0.357; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: GFR, glomerular filtration rate; RPGN, .

Hitachi creatinine auto-analyzer, model 7170 (Hitachi, Tokyo, Japan) and enzyme solution (Preauto-SCrE-N; Daiichi Pure Chemicals Co, Tokyo, Japan). SCr values obtained in the central laboratory were compared with those of the Cleveland Clinic (Cleveland, OH) by using a calibration panel of 40 samples, provided by Dr Frederick Van Lente, Cleveland Clinic.

Comparison of Measured Versus Expected Creatinine Excretion

Creatinine excretion was measured in 90-minute urine samples obtained during Cin measurements and predicted based on previously published formulas.

Creatinine excretion rates were based on published equations for Japenese[20] and whites[21] and are given in the notes to Table 2.

Development of the Correction Coefficient for the IDMS–MDRD Study Equation

The new Japanese coefficient to modify the IDMS–MDRD Study equation[7] for Japanese was calculated from the development data set of 413 participants. The coefficient was derived by minimizing the root mean squared error (RMSE) of the estimate calculated as the square root of (sum of squared errors of the estimate/[N]).

Development of the New Equations for Japanese

The new 3- and 5-variable Japanese equations were derived in the development data set by using a multiple linear regression model and the variables age, sex, and SCr, SUN, and serum albumin levels in relation to measured GFR (mGFR). All variables were log transformed.

Development of the Correction Coefficient for the CG Equation

The CG equation was modified by a Japanese CG coefficient that was calculated in the development data set. The correction coefficient was determined by minimizing the RMSEs of the estimate.

Validation of Equations

GFR was estimated by using all equations and compared with mGFR in the development and validation data

Table 2. Participant Characteristics

	Men (n = 462)	Women (n = 296)
Age (y)	53.7 ± 17.1	50.8 ± 16.8
Height (cm)	167.4 ± 7.1	154.9 ± 6.3
Weight (kg)	65.7 ± 11.9	52.7 ± 9.5
Body surface area (m^2)	1.74 ± 0.16	1.49 ± 0.13
Body mass index (kg/m^2)	23.4 ± 3.7	22.0 ± 3.8
Measured creatinine excretion (mg/kg/d)	20.2 ± 0.8	16.7 ± 4.6
Estimated creatinine excretion (for Japanese)	18.4 ± 1.2	14.3 ± 1.0
Estimated creatinine excretion (for whites)	19.0 ± 2.9	16.1 ± 1.9

Note: Data expressed as mean ± SD. Measured creatinine excretion was obtained during the measurement of inulin clearance. Expected creatinine excretion for Japanese was calculated by using the following equations: Creatinine excretion rate (mg/kg/d) = 22.1 − 0.068 × Age (in men) or 17.2 − 0.057 × Age (in women). Estimated creatinine excretion for whites was calculated by the following equations: Creatinine excretion rate (mg/kg/d) = 28.2 − 0.172 × Age (in men) or 21.9 − 0.115 × Age (in women).

sets. We compared all equations, but specifically focused on the comparison in the validation data set of the IDMS–MDRD Study equations modified by the previously published JSN Chronic Kidney Disease Initiative (JSN-CKDI) coefficient and the new Japanese coefficient, as well as the JSN-CKDI equation and new Japanese equations. Metrics for comparison were RMSE, bias, accuracy, and r^2. The RMSE of GFR estimated by using the equation was calculated as the square root of (sum of squared errors of the estimate/[N]). Bias of the equations was expressed as the mean difference between eGFR and mGFR (eGFR − mGFR). Accuracy was expressed as percentage of participants with eGFR less than 15% and 30% from mGFR. RMSE and correlation coefficients were computed on the raw scale. Data sets were combined for correlation between eGFR and mGFR. Intercepts and slopes were evaluated in a linear regression model.

Statistical Analysis

Data are expressed as mean ± SD. Measured versus predicted creatinine excretion was compared by using Student *t*-test. Creatinine values were calibrated by using the calibration panel and evaluated by means of linear regression. Differences in accuracy of eGFR were evaluated between equations by means of χ^2 tests. Differences in bias of eGFR were evaluated between equations by using Student *t*-test. A difference with *P* less than 0.05 was considered statistically significant. Statview, version 4.02 (SAS Institute, Cary, NC), and JMP, version 6.02 (SAS Institute), were used for statistical analysis and calculation of correction factors and confidence intervals (CIs).

RESULTS

Patient Characteristics in the Development and Validation Populations

Characteristics of the development population (n = 413) and validation population (n = 350) are listed in Table 1. Distributions of participant numbers by cause of kidney disease and mean age, SCr level, albumin level, SUN level, height, weight, and body surface area were similar between the 2 populations. Mean Cin was also similar between them at 59.1 ± 35.4 mL/min/1.73 m^2 in the development population and 57.2 ± 34.7 mL/min/1.73 m^2 in the validation population. Proportions of participants with mGFR less than 60 mL/min/1.73 m^2 were 54% in the development population and 60% in the validation population.

Body Size and Creatinine Excretion

Body size and creatinine excretion in the combined development and validation data sets are listed separately for men and women in Table 2. The creatinine excretion rate was greater in men than women (20.2 versus 16.7 mg/kg/d). Measured values were significantly, but not substantially, greater than expected values for both Japanese ($P < 0.001$) and whites ($P < 0.001$).

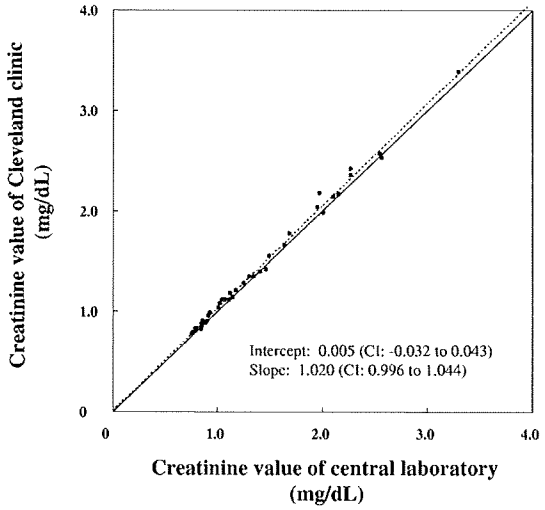

Figure 1. Correlation between creatinine values of the Cleveland Clinic and a central laboratory. Y = X (solid line), and regression line (dotted line). Abbreviation: CI, confidence interval.

Table 3. Intercepts and Coefficients for GFR-Estimating Equations in the Development Population

Equation	Exponent-Transformed Intercept (95% CI)	Coefficient of Continuous Parameters (95% CI)				Exponent-Transformed Coefficient Of Dichotomous Variables (95% CI)
		SCr	Age	SUN	Alb	
IDMS–MDRD Study	175	−1.154	−0.203	–	–	0.742 if female 1.01 if white 1.212 if black
1	175	−1.154	−0.203	–	–	0.742 if female 0.741 if Japanese
2	171	−1.004	−0.287	–	–	0.782 if female
3	175	−1.154	−0.203	–	–	0.742 if female 0.808 if Japanese (0.728 to 0.829)
4	194 (143 to 262)	−1.094 (−1.139 to −1.048)	−0.287 (−0.366 to −0.208)	–	–	0.739 if female (0.695 to 0.786)
5	142 (93 to 217)	−0.923 (−0.997 to −0.849)	−0.185 (−0.263 to −0.108)	−0.233 (−0.319 to −0.148)	0.414 (0.272 to 0.557)	0.772 if female (0.728 to 0.818)
6	–	–	–	–	–	0.85 if female (0.769 to 0.810)

Equation 1: IDMS–MDRD Study equation with previously reported JSN-CKDI coefficient: eGFR = $0.741 \times 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female).

Equation 2: Previously reported JSN-CKDI equation: eGFR = $171 \times SCr^{-1.004} \times Age^{-0.287} \times 0.782$ (if female).

Equation 3: IDMS–MDRD Study equation with new Japanese coefficient: eGFR = $0.808 \times 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female).

Equation 4: New 3-variable Japanese equation: eGFR = $194 \times SCr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female).

Equation 5: New 5-variable Japanese equation: eGFR = $142 \times SCr^{-0.923} \times Age^{-0.185} \times Alb^{0.414} \times SUN^{-0.233} \times 0.772$ (if female).

Equation 6: $0.789 \times$ CG equation: eGFR = $0.789 \times (140 - Age) \times BW/SCr/72 \times 1.73/BSA \times 0.85$ (if female).

Abbreviations: Alb, albumin; BSA, body surface area; BW, body weight; CG, Cockcroft-Gault; CI, confidence interval; CKDI, Chronic Kidney Disease Initiative; eGFR, estimated glomerular filtration rate; IDMS, isotope dilution mass spectrometry; JSN, Japanese Society of Nephrology; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine; SUN, serum urea nitrogen.

Calibration of Creatinine Assays

Creatinine values for the calibration panel assigned in our laboratory were compared with values assigned by Cleveland Clinic Laboratory (Fig 1). Mean SCr level was 1.415 ± 0.100 (SEM) versus 1.449 ± 0.102 mg/dL. Creatinine values correlated highly with values assigned by the Cleveland Clinic as judged by the intercept of 0.005 (95% CI, −0.0032 to 0.043), close to zero, and the slope of 1.020 (95% CI, 0.996 to 1.044), close to 1.0. Because there was no significant systemic bias, creatinine values were not adjusted in the present study.

Cin and Ccr

Cin and Ccr were measured simultaneously in 757 patients. Mean serum inulin concentrations were 18.4 ± 4.9, 18.3 ± 5.1, and 19.3 ± 5.9 mg/dL at 45, 75, and 105 minutes, respectively. The median coefficient of variation for Cin was 10.9% (95% CI, 5.8 to 20.4) during the 90-minute renal Cin test. The median coefficient of variation for Ccr was 13.3%. Cin and Ccr significantly correlated ($r = 0.889$; $r^2 = 0.790$). The slope was 0.698 (95% CI, 0.672 to 0.724) and the intercept was 2.339 (95% CI, 0.143 to 4.622). Ccr was significantly greater than Cin, and the correction coefficient for the bias was determined to be 0.715 (95% CI, 0.703 to 0.726).

eGFR Equations

All equations are listed in the notes to Table 3.

The new Japanese correction coefficient calculated for modification of the IDMS–MDRD Study equation was 0.808 (95% CI, 0.728 to 0.829; equation 3) in the development population, whereas the previously reported coefficient was 0.741 (equation 1), as listed in Table 3.

Using the development data set, we derived a new 3-variable Japanese equation (equation 4) and a new 5-variable Japanese equation (equation 5; Table 3).

Table 4. Performance of GFR-Estimating Equations in the Development Population

Equation	RMSE (mL/min/1.73 m^2)	Accuracy	
		Within 15% of mGFR (95% CI)	Within 30% of mGFR (95% CI)
IDMS–MDRD Study equation	23.6	36 (32-41)	59 (55-64)
Equation 1	18.4	38 (34-43)	73 (69-77)
Equation 2	19.2	39 (35-44)	73 (68-77)
Equation 3	17.6	44 (39-48)	77 (72-81)
Equation 4	17.3	44 (39-48)	78 (74-82)
Equation 5	16.4	52 (47-57)	83 (79-86)
Equation 6	17.7	44 (39-49)	76 (72-80)

P

15% Accuracy Level

	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5
IDMS						
Eq 1	0.6					
Eq 2	0.4	0.7				
Eq 3	0.03	0.1	0.2			
Eq 4	0.03	0.1	0.2	0.9		
Eq 5	<0.001	<0.001	<0.001	0.01	0.01	
Eq 6	0.03	0.1	0.2	0.9	0.9	0.02

30% Accuracy Level

	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5
IDMS						
Eq 1	<0.001					
Eq 2	<0.001	0.9				
Eq 3	<0.001	0.2	0.2			
Eq 4	<0.001	0.09	0.06	0.6		
Eq 5	<0.001	<0.001	<0.001	0.03	0.1	
Eq 6	<0.001	0.3	0.3	0.8	0.5	0.02

Note: Accuracy given as percentage of participants whose estimated GFR was within 15% or 30% of measured GFR.

Abbreviations: CI, confidence interval; Eq, equation; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease; RMSE, root mean squared error.

The CG equation was modified with a correction coefficient. The Japanese coefficient of 0.789 (95% CI, 0.769 to 0.810) was obtained from the development data set and is provided as equation 6 in Table 3.

Comparison of Performance of the Equations

Performance in GFR estimation was evaluated among equations by using the development and validation data sets based on RMSE, bias, and accuracy of eGFR in reference to mGFR.

Accuracy in the Development Data Set

Performance of each derived equation was evaluated by using the development data set, as listed in Table 4. Bias is not compared because it is expected to be approximately zero for equations developed in the development data set. There were no significant differences in accuracy within 15% or 30% between equations 3 and 1 or between equations 4 and 2, reflecting no significant different in precision.

Bias and Accuracy in the Validation Data Set

Performance of each derived equation was evaluated by using the validation data set, as listed in Table 5. Bias was significantly less in equation 3 than in equation 1 ($P = 0.002$) and in equation 4 than in equation 2 ($P < 0.001$). Equation 3 provided GFR with significantly better accuracy within 15% than equation 1 ($P = 0.02$), but no significant difference in accuracy within 30% deviation ($P = 0.6$) between the 2 equations. There was a trend toward improved accuracy within 15% and 30% between equations 4 and 2 ($P = 0.06$). Equation 5 performed similarly to equation 4.

Correlation Between eGFR and mGFR

The correlation between eGFR and mGFR was evaluated in the combined population as shown for each equation in Fig 2. Intercepts and slopes for equations are listed in Table 6.

DISCUSSION

We previously reported that eGFR calculated using either the IDMS–MDRD Study equation modified by using the JSN–CKDI coefficient (0.741; equation 1) or the JSN–CKDI equation (equation 2) was more accurate than the unmodified MDRD Study equation in Japanese individu-

Table 5. Performance of GFR-Estimating Equations in the Validation Population

Equations	RMSE (mL/min/1.73 m²)	Bias (mL/min/1.73 m²)	Accuracy	
			Within 15% of mGFR (95% CI)	Within 30% of mGFR (95% CI)
IDMS–MDRD Study equation	25.2	12.0 ± 22.2	39 (34-45)	59 (54-64)
Equation 1	19.9	−5.9 ± 19.0	34 (29-39)	72 (67-76)
Equation 2	20.3	−7.9 ± 18.7	36 (31-41)	73 (69-78)
Equation 3	19.4	−1.3 ± 19.4*	43 (38-48)	73 (59-78)
Equation 4	19.1	−2.1 ± 19.0†	43 (38-48)	75 (70-79)
Equation 5	17.7	−1.2 ± 17.6	49 (44-54)	79 (75-83)
Equation 6	19.4	−1.7 ± 19.6	45 (40-50)	75 (70-79)

P

15% Accuracy Level						
	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5
IDMS						
Eq 1	0.1					
Eq 2	0.4	0.5				
Eq 3	0.4	0.02	0.08			
Eq 4	0.3	0.01	0.06	0.9		
Eq 5	0.01	<0.001	<0.001	0.1	0.1	
Eq 6	0.1	0.003	0.02	0.5	0.6	0.3

30% Accuracy Level						
	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5
IDMS						
Eq 1	<0.001					
Eq 2	<0.001	0.6				
Eq 3	<0.001	0.6	0.9			
Eq 4	<0.001	0.3	0.06	0.6		
Eq 5	<0.001	0.02	0.08	0.08	0.2	
Eq 6	<0.001	0.3	0.7	0.7	0.9	0.2

Note: Accuracy given as percentage of participants whose estimated GFR was within 15% or 30% of measured GFR.

Abbreviations: CI, confidence interval; Eq, equation; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease; RMSE, root mean squared error.

als.[19] The present study verifies our previous results, and accuracy of GFR estimation is improved further by means of newly derived equations, the modified IDMS–MDRD Study equation with the new Japanese coefficient (0.808; 95% CI, 0.728 to 0.829; equation 3) and the new 3-variable equation (equation 4). Bias was significantly reduced in equation 3 and 4 from that in equations 1 and 2 in the validation population. We also developed a 5-variable equation (equation 5). The new Japanese equations and the new Japanese coefficient for the IDMS–MDRD Study equation provided more reliable eGFRs in Japanese individuals. The present study had a larger number of participants than the previous study, and all samples were assayed for inulin and creatinine in a central laboratory.

In both the previous[18,19] and present studies, the original IDMS–MDRD Study equation overestimated GFR in comparison to mGFR by using Cin in Japanese patients with CKD (Fig 2). The correction coefficient less than 1.0 indicates lower SCr levels in Japanese than in whites in the MDRD Study for equivalent levels of GFR.

SCr level is affected by 3 major factors: level of kidney function, skeletal muscle mass,[2] and amount of protein intake.[22] In the steady state, creatinine excretion is a measure of creatinine generation from muscle or protein intake. Our data suggest that creatinine excretion was slightly greater than expected per kilogram of body weight, but less than observed in the MDRD Study because of lower body weight. Mean creatinine excretion values were 20.2 and 16.7 mg/kg/d in men and women in our study compared with 19.2 and 15.8 mg/kg/d in the MDRD Study, respectively.[23] Mean body weight was 60 kg in our study compared with 79 kg in the MDRD Study. Mean body mass index (BMI) was 23 kg/m² in the present study and 27 kg/m² in the MDRD Study.[23]

Differences in creatinine excretion, body weight, and BMI between participants in our study and the MDRD Study are consistent with studies that have shown a mean skeletal muscle mass assessed by means of magnetic resonance imaging data significantly less in Japanese (men, 24.8 ± 3.5 kg; women, 14.7 ± 2.3 kg)[24] than in North Americans (men, 33.0 ± 5.3 kg; women,

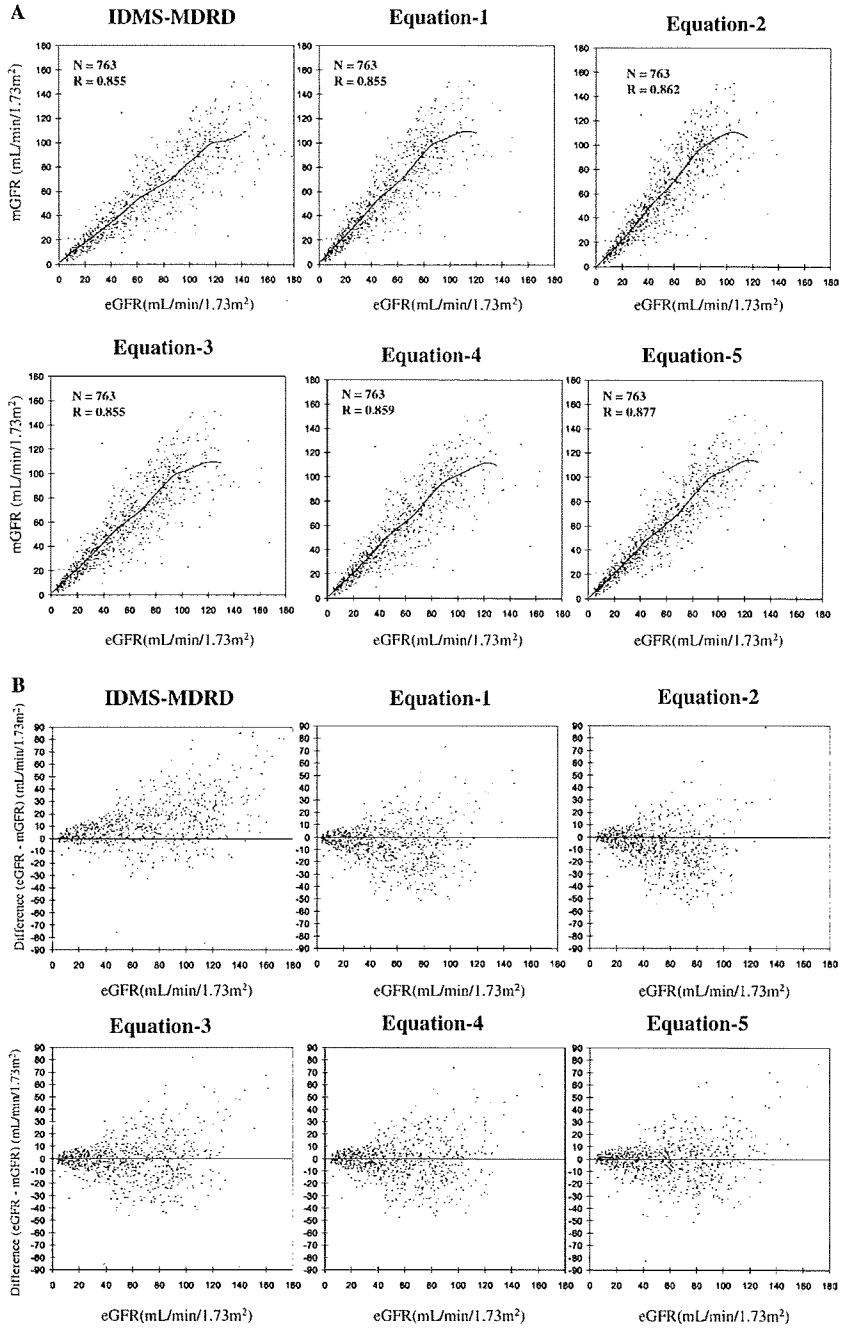

Figure 2. Correlation between estimated glomerular filtration rate (eGFR) using each equation and measured GFR (mGFR) in the combined population. (A) mGFR versus eGFR and (B) eGFR minus mGFR versus eGFR. Smoothed lines show the fit of the data. Abbreviations: IDMS-MDRD, isotope dilution mass spectrometry Modification of Diet in Renal Disease.

21.0 ± 3.8 kg; study population included whites [67%], blacks [17%], Asians [8%], and Hispanics [7%]).[25]

These differences in muscle mass are reflected as differences in SCr levels between Japanese and North American populations. Muscle mass significantly decreases with aging in Japanese men,[24] but does not significantly change in North American men.[25] SCr values were lower and remained constant until age 70 years in Japanese for both men and women,[26] whereas values were greater and increased after age 40 years in whites and blacks[27]: 0.831 mg/dL at age 20 to 39 years, 0.822 mg/dL at age 40 to 59 years, and 0.868 mg/dL at age 60 to 79 years in Japanese men versus 0.865 mg/dL at age 20 to 39 years, 0.883

Table 6. Intercepts and Slopes for GFR-Estimating Equations

Equations	Intercept (95% CI)	Slope (95% CI)	*R2*
IDMS–MDRD Study equation	6.1 (3.5 to 8.6)	0.740 (0.708 to 0.771)	0.731
Equation 1	6.1 (3.5 to 8.6)	0.998 (0.955 to 1.041)	0.731
Equation 2	1.8 (−0.9 to 4.5)	1.123 (1.076 to 1.170)	0.743
Equation 3	6.1 (3.5 to 8.6)	0.915 (0.876 to 0.955)	0.731
Equation 4	5.1 (2.5 to 7.7)	0.943 (0.903 to 0.983)	0.738
Equation 5	4.5 (2.1 to 6.9)	0.944 (0.907 to 0.980)	0.770
Equation 6	6.7 (4.1 to 9.3)	0.908 (0.869 to 0.948)	0.730

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease.

mg/dL at age 40 to 59 years, and 0.998 mg/dL at 60 years and older as calibrated to IDMS-traceable creatinine in white men. Mean noncalibrated SCr values in the Third National Health and Nutrition Examination Survey (NHANES III) were 1.14 mg/dL at age 20 to 39 years, 1.16 mg/dL at age 40 to 59 years, and 1.28 mg/dL at 60 years and older[28] in white men (calibrated SCr = [SCr − 0.23] × 0.95).[29,30] After age 50 years, urinary creatinine excretion decreases as body weight decreases in Japanese men. However, in whites body weight is not as good a marker to estimate urinary creatinine excretion as muscle mass. Lean body mass, not body weight, correlates with urinary creatinine excretion and muscle mass in whites.[31]

Differences in muscle mass are parallel to differences in obesity. The obese population (BMI > 25 kg/m^2) increases with age in white Americans: 61% at age 20 to 39 years, 70% at age 40 to 59 years, and 74% at 60 years and older.[32] However, obesity decreases after age 50 years in Japanese men: BMI greater than 25 kg/m^2 is 20% at age 20 to 29 years, 28.9% at age 30 to 39 years, 32.7% at age 40 to 49 years, 30.8% at age 50 to 59 years, 29.7% at age 60 to 69 years, and 26% at 70 years and older (Japanese Ministry of Health, Labor, and Welfare). It was reported that an increase of 5 kg/m^2 in BMI resulted in increase of 1.1% in SCr level.[33] With aging, skeletal muscle mass and protein intake decrease at a greater rate in Japanese than in whites, whereas the prevalence of obesity increases in whites, but not Japanese.

Altogether, these data are consistent with a correction coefficient less than 1.0 for modification of the MDRD Study equation for Japanese. In contrast, the correction coefficient for Chinese is 1.233. Possible explanations for the large difference in correction coefficients between Japanese and Chinese studies may be differences in muscle mass in the study populations, creatinine assays, or GFR measurement methods. Additional study is required to understand the difference in GFR-estimating equations between Chinese and Japanese.

In the present study, no significant systemic bias was observed in SCr values used for the development of new equations by the panel of the Cleveland Clinic Laboratory. SCr values assayed using the enzymatic method were more accurate and had greater precision than other methods.[2] Although 95% of laboratories in Japan have switched to the enzymatic method from the Jaffé method, creatinine values must be standardized for use of the new equations.

Limitations of the present study are as follows. (1) The new Japanese GFR-estimating equations may not be applicable to the healthy population because they were derived mostly from patients with chronic kidney disease. Rule et al[10] also suggested that the MDRD Study equation might systematically underestimate GFR in the normal healthy population. (2) Equations were derived from data for inpatients and outpatients. Some participants were hospitalized for renal biopsy as is customary practice in Japan, although some inpatient participants may have had clinical conditions related to creatinine metabolism.[14] (3) About 15% of patients had diabetes, and GFR was estimated accurately for patients with diabetes with our new equations. However, GFRs calculated by using the MDRD Study equation and CG equations were underestimated in patients with diabetes over the range of eGFR of 90 mL/min/1.73 m^2 or greater.[34] We must further

study the accuracy of eGFR in Japanese patients with diabetes.

In conclusion, according to Cin data, the newly derived creatinine-based GFR-estimating equations accurately estimate GFR for Japanese. Although the 5-variable Japanese equation estimates GFR more accurately than other equations, SUN and albumin are not routinely measured in Japan. Because the new 3-variable Japanese equation provided reasonably accurate eGFRs, we recommend using the new 3-variable Japanese equation for GFR estimation from SCr level and age in clinical practice and for epidemiological study.

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ORIGINAL ARTICLE

Prevalence of chronic kidney disease in the Japanese general population

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Abstract
Background We previously estimated the prevalence of chronic kidney disease (CKD) stages 3–5 at 19.1 million based on data from the Japanese annual health check program for 2000–2004 using the Modification of Diet in Renal Disease (MDRD) equation multiplied by the coefficient 0.881 for the Japanese population. However, this equation underestimates the GFR, particularly for glomerular filtration rates (GFRs) of over 60 ml/min/1.73 m^2. We did not classify the participants as CKD stages 1 and 2 because we did not obtain proteinuria data for all of the participants. We re-estimated the prevalence of CKD by measuring proteinuria using a dipstick test and by calculating the GFR using a new equation that estimates GFR based on data from the Japanese annual health check program in 2005.

This work was presented in part at the 50th Annual Meeting of the Japanese Society of Nephrology at Fukuoka in 2008.

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Methods Data were obtained for 574,024 (male 240,594, female 333,430) participants over 20 years old taken from the general adult population, who were from 11 different prefectures in Japan (Hokkaido, Yamagata, Fukushima, Tochigi, Ibaraki, Tokyo, Kanazawa, Osaka, Fukuoka, Miyazaki and Okinawa) and took part in the annual health check program in 2005. The glomerular filtration rate (GFR) of each participant was computed from the serum creatinine value using a new equation: GFR (ml/min/1.73 m^2) = 194 × $Age^{-0.287}$ × $S\text{-}Cr^{-1.094}$ (if female × 0.739). The CKD population nationwide was calculated using census data from 2005. We also recalculated the prevalence of CKD in Japan assuming that the age composition of the population was same as that in the USA.

Results The prevalence of CKD stages 1, 2, 3, and 4 + 5 were 0.6, 1.7, 10.4 and 0.2% in the study population, which resulted in predictions of 0.6, 1.7, 10.7 and 0.2 million patients, respectively, nationwide. The prevalence of low GFR was significantly higher in the hypertensive and proteinuric populations than it was in the populations without proteinuria or hypertension. The prevalence rate of CKD in Japan was similar to that in the USA when the Japanese general population was age adjusted to the US 2005 population estimate.

Conclusion About 13% of the Japanese adult population—approximately 13.3 million people—were predicted to have CKD in 2005.

Keywords Chronic kidney disease · Japanese · eGFR · Serum creatinine

Introduction

The number of chronic dialysis patients has been increasing over the last three decades in Japan, and it reached to 275,119 in 2007 [1]. The number of new dialysis patients has continuously increased, and 36,909 patients developed end-stage kidney disease (ESKD) in 2007 [1]. The latent chronic kidney disease (CKD) population therefore appears to be enormous in Japan. In addition, a growing body of evidence suggests that individuals with CKD are at high risk of cardiovascular disease (CVD) [2–4]. Thus, in order to gain a deeper knowledge of the target CKD population for better public policy making and government administration of medical affairs, it is necessary to estimate the prevalence of CKD in Japan with a nationwide epidemiological study.

In our previous study, we estimated the prevalence of CKD stages 3–5 at 19.1 million [5] based on data from the Japanese annual health check program in 2000–2004 using the MDRD equation multiplied by a coefficient of 0.881 for the Japanese population. However, this underestimates GFR, particularly for GFRs of over 60 ml/min/1.73 m^2 [6]. Therefore, the prevalence of CKD may be overestimated when using this equation. The creatinine was measured by an enzymatic method as well as by the uncompensated Jaffe method during that time period, and we corrected the creatinine to the uncompensated Jaffe method. In addition, we did not classify the participants as CKD stage 1 or 2 because we did not correct the data on proteinuria for all of the participants.

The Japanese Society of Nephrology recently established an equation for estimating GFR from serum creatinine and age for the Japanese general population [7]. The new equation provides reasonably accurate estimated GFR (eGFR) values for clinical practice and epidemiological study.

In this study, we used the new Japanese equation for estimating GFR, and the data were sampled from over half a million members of the general population who participated in an annual health check-up program in 2005 conducted in 11 prefectures of Japan; serum creatinine levels were calibrated against a central laboratory.

Methods

Study population

In this study, serum creatinine values were obtained from 574,024 members of the adult population (male 240,594, female 333,430) who participated in a large-scale annual health check-up program that was conducted in 11 prefectures of Japan (Hokkaido, Yamagata, Fukushima, Tochigi, Ibaraki, Tokyo, Kanazawa, Osaka, Fukuoka, Miyazaki and Okinawa) in 2005. All of the participants remained anonymous and the study was conducted according to Japanese privacy protection laws and ethical guidelines for epidemiological study published by the Ministry of Education, Science and Culture and the Ministry of Health, Labor and Welfare in 2005.

Calibration of serum creatinine values

Serum samples were assayed by an enzymatic method in all participating laboratories. To calibrate the samples, ten laboratories measured the calibration panel of 40 samples that was kindly provided by Dr. Frederic van Lante, Cleveland Clinic (Cleveland, Ohio). The creatinine values obtained in each laboratory were compared with the IDMS-traceable value at Cleveland Clinic (Cleveland, Ohio).

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The serum creatinine values measured at each local laboratory (X) were corrected to the IDMS-traceable value obtained at Cleveland Clinic by the following formulae:

Miyazaki: $Y = 1.0617\ X - 0.1128$
Yamagata: $Y = 1.0543\ X - 0.0482$
Tochigi: $Y = 0.9558\ X + 0.0851$
Okinawa: $Y = 1.0176\ X - 0.0644$
Tokyo: $Y = 1.0595\ X - 0.0760$
Ibaraki: $Y = 1.0356\ X + 0.0074$
Hokkaido: $Y = 1.0418\ X + 0.0600$
Fukushima: $Y = 1.0429\ X - 0.0625$

Data from Ishikawa, and Osaka were not corrected because their data were accurate enough to be used without correction. Data from Fukuoka were not corrected on procedural grounds.

Estimation of GFR using the new Japanese equation for estimated GFR from serum creatinine

The GFR of each participant was calculated from their serum creatinine value (SCr) and their age using the new Japanese equation as follows [7]:

$$\text{GFR (ml/min/1.73 m}^2) = 194 \times \text{Age}^{-0.287} \times \text{S-Cr}^{-1.094} \text{ (if female} \times 0.739)$$

Evaluation of renal function and estimation of CKD prevalence

Renal function was evaluated in each participant using the estimated GFR. The prevalence of CKD was calculated for CKD stages 1, 2, 3, and 4 + 5, defined as GFR ≥90, 89–60, 30–59, and <30 ml/min/1.73 m^2, respectively. The age-specific prevalence of CKD stages 3–5 (ages 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and above 80 years) were calculated for each sex for the study population. The prevalence of CKD was also estimated for the general adult population using data on the Japanese adult population (103.2 million) obtained from a census in 2005 [8].

Comparison of the prevalence of CKD in Japan with that in the USA

The Japanese demographic statistics used were the population estimates from the census in 2005 [8].

The prevalence of CKD in the general population was reported on the basis of the National Health and Nutrition Examination Survey (NHANES 1999–2004, $n = 13233$) in the USA [9]. The demographic statistics for the USA that were used were the population estimates from a census from 2005 conducted by the Population Projections Branch, US Census Bureau (11 May 2004) [10].

Prevalence of CKD among hypertensive, proteinuric and diabetic populations

Proteinuria was defined as a urinary protein excretion of 1+ or more by dipstick test. Hypertension was defined as a blood pressure of 140/90 mmHg or more. The diabetic population was defined as having HbA1c ≥6.0%. The age-specific prevalence of CKD in the hypertensive proteinuric and diabetic populations were compared with those in the populations without hypertension, without proteinuria, and with HbA1c <6.0%, respectively.

Distribution of GFR in diabetic and nondiabetic populations

The distribution of estimated GFR in diabetic patients with HbA1c >6.0% was compared with that in patients with HbA1c <6.0%.

Statistics

Prevalence of proteinuria, hypertension and diabetes are expressed as percentages (%) with respect to the age-specific study population. The prevalences in males and females were compared by chi-square test. A P value of less than 0.05 was considered statistically significant. Age-specific prevalences of CKD stages are expressed as percentages (%) with respect to the age-specific study population with a 95% confidence interval (CI). The prevalences of CKD for subjects with complications such as hypertension, proteinuria and high HbA1c were compared with the prevalences in subjects without these complications by chi-square test.

Results

Prevalence of proteinuria, hypertension and diabetes in the Japanese general population

The prevalence of dipstick proteinuria (1+ or more) is shown in Fig. 1A. The prevalence of proteinuria in males increased from about 1.7 to 8.7% depending on age, while that in females remained approximately 2% (1.6–2.3%) until age reached the 70. Prevalence of hypertension, as defined by a blood pressure of 140/90 mmHg or more, increased from 5.1 to 41.5% as age increased from the 20s to the 80s in male subjects, while the prevalence also increased from 0.7 to 45.0% in females, although to a lesser extent until the 60s (Fig. 1B). Prevalence of diabetes, as defined by HbA1c >6.0%, increased from 0.2 to 12.9% as age increased from the 20s to 70s in males, while that in females also increased with age, although to a lesser extent (Fig. 1C).

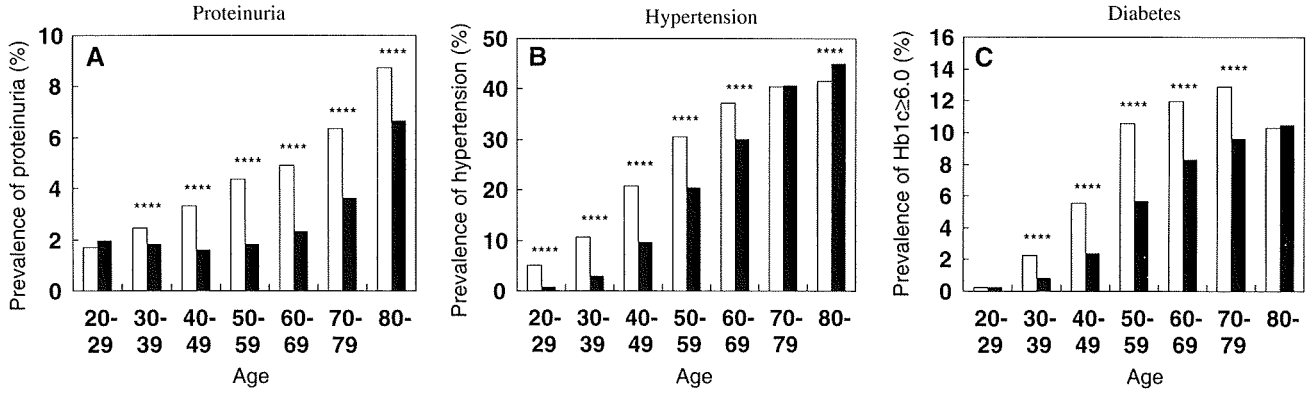

Fig. 1 Prevalence of proteinuria, hypertension, and diabetes in the study population. Proteinuria was defined as 1+ or more by dipstick test (**a**). Hypertension was defined as a systolic blood pressure of ≥40 mmHg, or a diastolic pressure of ≥90 mmHg (**b**). Diabetes was defined as HbA1c ≥6.0% (**c**). *White columns* male, *black columns* female. ****$p < 0.0001$ versus female

Table 1 Age-specific prevalence of chronic kidney disease (CKD) stages in males

	Age						
	20–29	30–39	40–49	50–59	60–69	70–79	80 and over
GFR ≥90 ml/min/1.73 m^2							
N	5166	8684	7325	9056	7714	3374	539
Prevalence (%)	52.7	37.4	20.1	17.1	13.2	6.7	5.0
95% CI	51.7–53.7	36.8–38.1	19.7–20.5	17.4–18.1	12.9–13.4	6.5–6.9	4.6–5.4
GFR 60–89 ml/min/1.73 m^2							
N	4629	14295	27704	38167	41638	33190	5455
Prevalence (%)	47.2	61.6	75.9	74.8	71.0	65.6	50.4
95% CI	46.2–48.2	61.0–62.3	75.5–76.4	74.4–75.1	70.6–71.4	65.2–66.0	49.4–51.3
GFR 50–59 ml/min/1.73 m^2							
N	5	187	1290	3209	7030	9469	2864
Prevalence (%)	0.1	0.8	3.5	6.3	12.0	18.7	26.4
95% CI	0.0–0.1	0.7–0.9	3.4–3.7	6.1–6.5	11.7–12.3	18.4–19.1	25.6–27.3
GFR 40–49 ml/min/1.73 m^2							
N	4	17	107	439	1811	3476	1353
Prevalence (%)	0.0	0.1	0.3	0.9	3.1	6.9	12.5
95% CI	0.0–0.1	0.0–0.1	0.2–0.4	0.8–0.9	3.0–3.2	6.7–7.1	11.9–13.1
GFR 30–39 ml/min/1.73 m^2							
N	0	4	21	84	306	784	456
Prevalence (%)	0.0	0.0	0.1	0.2	0.5	1.5	4.2
95% CI	0.0–0.0	0.0–0.0	0.0–0.1	0.1–0.2	0.5–0.6	1.4–1.7	3.8–4.6
GFR <30 ml/min/1.73 m^2							
N	3	6	31	88	141	312	161
Prevalence (%)	0.0	0.0	0.1	0.2	0.2	0.6	1.5
95% CI	0.0–0.1	0.0–0.1	0.1–0.1	0.1–0.2	0.2–0.3	0.6–0.7	1.3–1.7

Prevalence of CKD in Japan

Age-specific percentages of specific GFR ranges (age <30, 30–39, 40–49, 50–59, 60–79 and ≥80 ml/min/1.73 m^2) in the study population indicated that the prevalence rate of low GFR increased with age (Tables 1, 2). The prevalences of CKD stage 3 and stages 4 + 5 in each age group are shown for each sex in Fig. 2. The prevalence of CKD stage 3 (GFR 40–59 ml/min/1.73 m^2), in particular, increased with age.

The prevalence rates of CKD stages 1, 2, 3, 4 + 5 in the Japanese population in 2005 were 0.6, 1.7, 10.4, and 0.2%, respectively (Table 3). The total predicted number of cases

Table 2 Age-specific prevalence of chronic kidney disease (CKD) stages in females

	Age						
	20–29	30–39	40–49	50–59	60–69	70–79	80 and over
GFR ≥90 ml/min/1.73 m^2							
N	7032	11161	17685	17819	7514	4633	681
Prevalence (%)	67.2	53.3	34.1	22.1	8.6	6.9	4.7
95% CI	66.3–68.1	52.7–54.0	33.7–34.5	21.8–22.4	8.4–8.8	6.7–7.1	4.4–5.0
GFR 60–89 ml/min/1.73 m^2							
N	3402	9575	32834	57354	67071	41410	7139
Prevalence (%)	32.5	45.8	63.3	71.1	76.6	61.4	49.2
95% CI	31.6–33.4	45.1–46.4	62.9–63.7	70.8–71.4	76.4–76.9	61.0–61.7	48.4–50.0
GFR 50–59 ml/min/1.73 m^2							
N	19	168	1206	4822	10601	15859	3385
Prevalence (%)	0.2	0.8	2.3	6.0	12.1	23.5	23.3
95% CI	0.0–0.3	0.7–0.9	2.2–2.5	5.8–6.1	11.9–12.3	23.2–23.8	22.6–24.0
GFR 40–49 ml/min/1.73 m^2							
N	2	13	98	521	1939	4333	2367
Prevalence (%)	0.0	0.1	0.2	0.6	2.2	6.4	16.3
95% CI	0.0–0.1	0.0–0.1	0.2–0.2	0.6–0.7	2.1–2.3	6.2–6.6	15.7–16.9
GFR 30–39 ml/min/1.73 m^2							
N	1	2	20	80	263	927	710
Prevalence (%)	0.0	0.0	0.0	0.1	0.3	1.4	4.9
95% CI	0.0–0.0	0.0–0.0	0.0–0.1	0.1–0.2	0.5–0.6	1.4–1.7	3.8–4.6
GFR <30 ml/min/1.73 m^2							
N	1	5	16	79	133	318	232
Prevalence (%)	0.0	0.0	0.0	0.1	0.2	0.5	1.6
95% CI	0.0–0.0	0.0–0.1	0.1–0.1	0.1–0.1	0.1–0.2	0.4–0.5	1.4–1.8

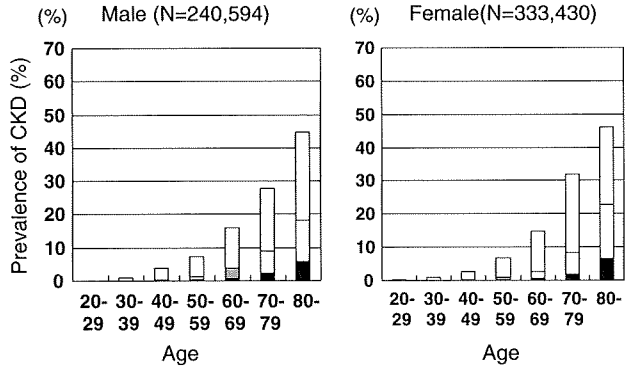

Fig. 2 Prevalence rates for CKD stages 3 to 5 for each age group in males and females in the study population. The prevalence of CKD (%) (as defined by <60 ml/min/1.73 m^2) for each age group was calculated separately for males and females in the study population. *White column* GFR 50–59 ml/min/1.73 m^2, *striped column* GFR 40–49 ml/min/1.73 m^2, *black column* GFR 40 or less ml/min/1.73 m^2

of CKD stages 1, 2, 3, 4 + 5 in the Japanese adult population in 2005 were 0.61, 1.71, 10.74, and 0.23 million, respectively (Table 3).

Prevalence of CKD stages 3–5 in proteinuric and hypertensive populations

The prevalence of CKD stages 3–5 was examined in proteinuric and hypertensive populations (Fig. 3A, B). The prevalence of CKD stages 3–5 was significantly higher in subjects with proteinuria ($P < 0.0001$) in all age groups, and in subjects with hypertension ($p < 0.01$ to $p < 0.0001$) in all age groups except for 80 years or older and in females in their 20s.

Prevalence of CKD stages 3–5 in the diabetic population

The prevalence of CKD stages 3–5 was examined in subjects with HbA1c ≥6.0 (Fig. 3C). The prevalence of CKD (defined as GFR <60 ml/min/1.73 m^2) was significantly lower in the diabetic population in some age groups (Fig. 3C), while its prevalence in subjects with reduced renal function (GFR <40 ml/min/1.73 m^2) was significantly higher in diabetic individuals in their 50s and 60s (Fig. 3D).

Table 3 Prevalence rates of CKD stages in Japanese adults (20 years or older), and estimated number of CKD cases per CKD stage based on the 2005 census

GFR (ml/min/1.73 m^2)	Total	Proteinuria (+)	Proteinuria (−)
Prevalence rate (%)			
GFR ≥90	27.8	0.6	27.2
60–89	61.6	1.7	60.0
30–59	10.4	0.8	9.6
<30	0.2	0.1	0.1
Stage 3			
50–59	7.6	0.4	7.2
40–49	2.3	0.3	2.0
30–39	0.6	0.1	0.4
Estimated number of Japanese adults in 2005			
GFR ≥90	28639274	605313	28033961
60–89	63576938	1708870	61868068
30–59	10743236	8238881	9919355
<30	236569	125190	111379
Stage 3			
50–59	7809261	425146	7384116
40–49	2363987	267158	2096828
30–39	569988	131577	438411

Prevalence of hyperfiltration in the diabetic population

The prevalence of subjects with GFR ≥120 ml/min/1.73 m^2 was significantly higher in the diabetic population ($p < 0.05$ to $p < 0.0001$) at ages 30–79 (Fig. 4). The distribution of GFR in the diabetic population was shifted to higher values than for the population with HbA1c <6.0%. A representative figurefor ages 50–59 is shown in Fig. 5. The prevalence of hypertension with GFR ≥120 ml/min/1.73 m^2 was significantly higher in the diabetic population ($p < 0.0001$) compared with the nondiabetic population (Fig. 5).

Comparison of GFR in the general population between Japan and the USA

The distribution of GFR across the whole Japanese population, calculated on the basis of the census from 2005, is shown in Fig. 6. Japan is an aging society, and the age pyramid for the population is shifted towards the elderly. An aging population tends to have low GFR, and this aging affects the distribution of GFR in the country. We recalculated the distribution of GFR by age adjusting the Japanese population to the 2005 US population estimate. As shown in Fig. 6, the distribution of GFR in the Japanese population is shifted to higher values after the correction for aging affects.

Discussion

In this study, we examined the prevalence of CKD for participants in a nationwide annual health check program in 11 prefectures of Japan using a new equation for estimating GFR from serum creatinine in the Japanese population [7]. The prevalence rates of CKD stages 1, 2, 3, and 4 + 5 in the study population of 574,024 were 0.6, 1.7, 10.4 and 0.2%, which resulted in predictions of 0.6, 1.7, 10.7 and 0.2 million patients, respectively, nationwide based on the census from 2005. Proteinuria resulted in a preponderance of declining GFR. The prevalence of concurrent CKD was significantly higher in the hypertensive population than in the population without hypertension, particularly in males. The diabetic population showed a preponderance of hyperfiltration, defined as GFR ≥120 ml/min/1.73 m^2.

The prevalence of CKD stages 1–5 has been reported for several countries (Fig. 7). According to the reliable and unbiased NHANES III surveys conducted from 1988 to 1994, from 1999 to 2000 [11], and from 1999 to 2004 [9], the prevalence of CKD remained the same between the first two surveys but increased for the third screening. For CKD stages 3 and stage 4, the prevalences were 4.2 and 0.19% in the first survey and 3.7 and 0.13% in the second survey, respectively [11]. In the third survey, the prevalences of CKD stages 1, 2, 3, 4 were 1.78, 3.24, 7.69, 0.35%, respectively (Fig. 7) [9], suggesting that the prevalence rates of CKD stages 3 and 4 increased in the USA. In Nord-Trondelag, a county in Norway, the prevalences were 4.2% for CKD stage 3 and 0.2% for CKD stages 4 + 5 [12]. The reported prevalence of CKD varies among countries in Asia. In Taiwan, about half a million participants were examined, and the MDRD equation was applied without correction using an ethnic coefficient; here, the prevalence rate of CKD was 11.9%, and those for CKD stages 1, 2, 3, 4, and 5 were 1.0, 3.8, 6.8, 0.2, 0.1%, respectively [13]. In Beijing, China, the prevalence of CKD was obtained using the original Chinese equation for estimating GFR, and the prevalences of CKD stages 1, 2, 3, 4 and 5 were 5.5, 3.3, 1.3, 0.0010 and 0.0003%, respectively [14]. Overall, about 10–13% of the population exhibited CKD in these countries. The different prevalences of CKD stages 1 and 2 among the countries appears to be mainly due to how proteinuria is defined. The definition of albuminuria differed considerably between countries. China defined albuminuria as 17 mg/g Cr [14], while the USA defined it as 30 mg/g Cr [9]. Taiwan defined proteinuria as (±) on dipstick test [13], while Japan defined a dipstick of (1+) as proteinuria. This difference in definition must affect the the prevalences of CKD stages 1 and 2 considerably. In addition, the methods used for creatinine measurement varied considerably among countries. We advocate the use of the

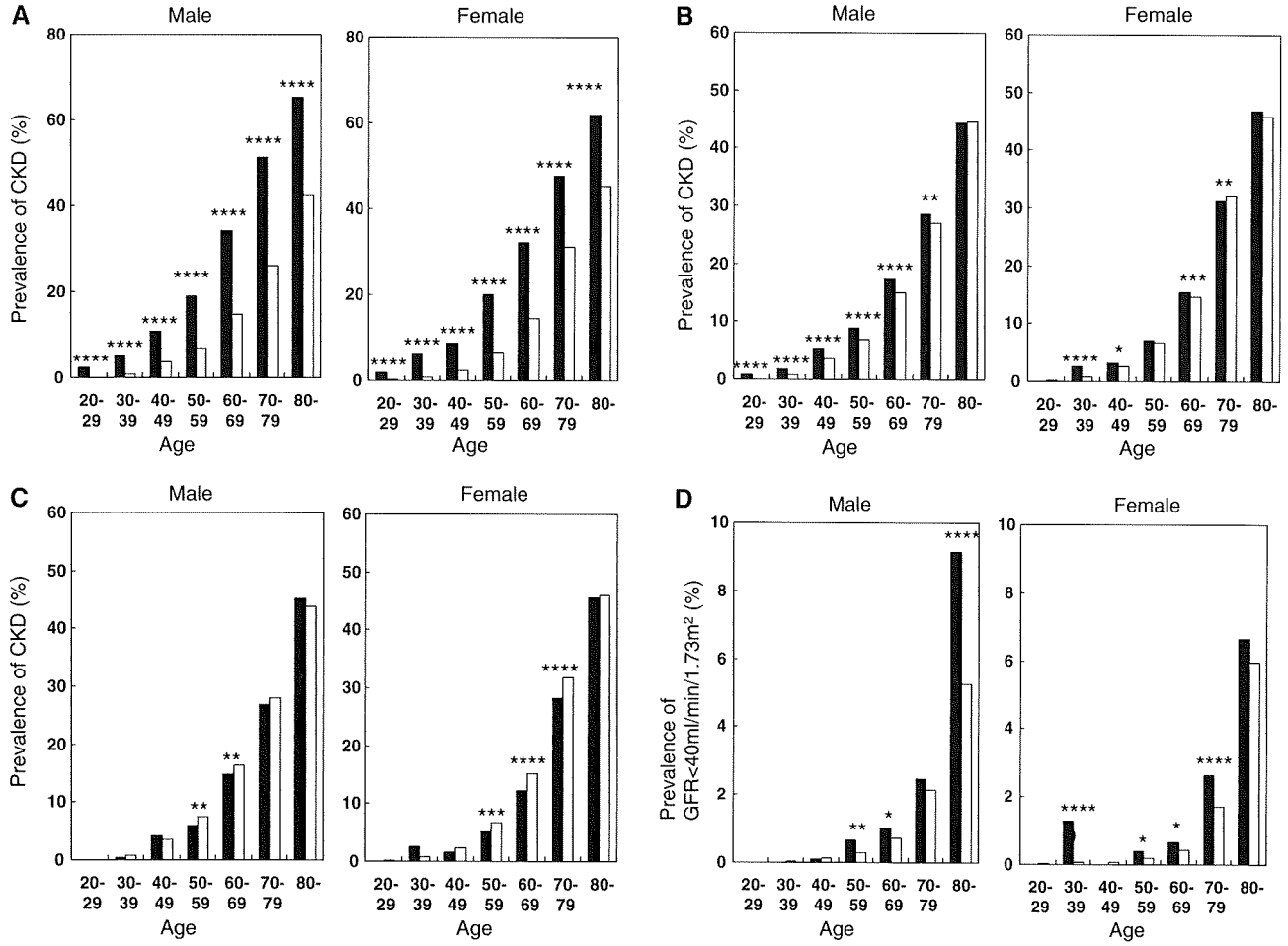

Fig. 3 Prevalence of CKD in proteinuria, hypertensive and diabetic populations. The prevalence of CKD (defined by GFR <60 ml/min/1.73 m^2) in the proteinuric population, shown by the *black column*, was compared with that in the population without proteinuria, shown by the *white column*, for each generation (**a**). Proteinuria was defined as 1+ or more by dipstick test. Prevalence of CKD (defined as GFR <60 ml/min/1.73 m^2) in the hypertensive population, shown by the *black column*, was compared with that in the population without hypertension, shown by the *white column*, for each generation (**b**). Hypertension was defined as a blood pressure of 140/90 mmHg or over. Prevalences of GFR <60 ml/min/1.73 m^2 and of GFR <40 ml/min/1.73 m^2 in the diabetic population (*black columns*) are compared with that in the nondiabetic population (*white columns*) (**c**, **d**). Diabetes was defined as HbA1c ≥6.0%. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$ versus individuals without cormobidity of proteinuria (**a**), hypertension (**b**), or diabetes (**c**, **d**)

following in order to compare the prevalence of CKD among different countries. First, the definition and method of measuring proteinuria must be unified across countries. Albuminuria or albuminuria-to creatinine ratio, which is scientifically more reliable than the dipstick test, should be used for proteinuria. Repeated measurements are recommended. Second, the serum creatinine that is used to estimate GFR should be measured by isotope diluted mass spectrometry (IDMS)-traceable creatinine assay. Third, the equation used to estimate GFR for each ethnic group must be established. Another alternative is to establish an IDMS-traceable MDRD equation [15] with an ethnic coefficient. The measurement of proteinuria by dipstick test and serum creatinine is accurate enough for daily practice and screening, but international comparisons of the prevalence of CKD should be done by a unified standard method involving the measurement of albuminuria and serum creatinine with an IDMS-traceable creatinine assay.

Our aging society results in a decline in the average GFR in this country. More than 20% of the Japanese population is over 60 years old, and the elderly population (over 75 years old) is much higher than in other countries. Because of this increased average age, the prevalence of CKD is higher in Japan. In fact, the distribution of the age-adjusted eGFR was shown to be similar for Japan and the USA (Fig. 6).

The prevalence of proteinuria increased as GFR decreased (Table 3) in this study. However, the prevalences of proteinuria in CKD stages 3 and 4 + 5 were 7.7 and 52.9%, respectively. In data from a mass health

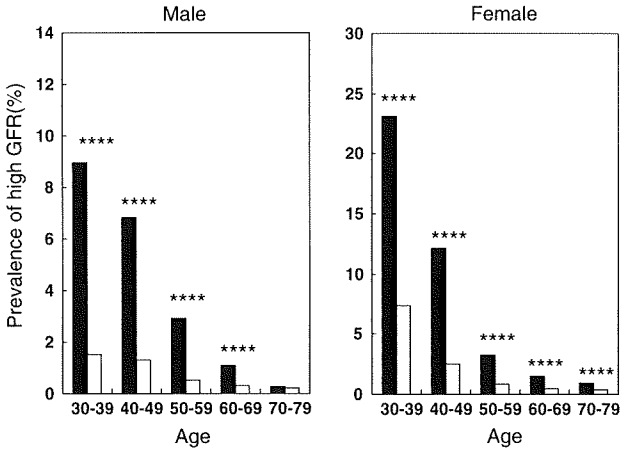

Fig. 4 Prevalence of GFR ≥120 ml/min/1.73 m^2 in the diabetic population. Individuals with diabetes as defined by HbA1c ≥6.0% are represented by the *black column*. Individuals with HbA1c <6.0% are represented by the *white column*. ****$p < 0.0001$ versus individuals with HbA1c <6.0%

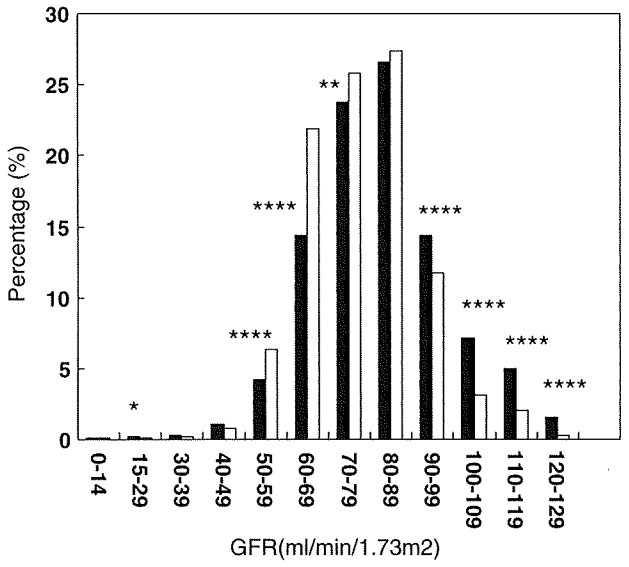

Fig. 5 Distribution of estimated GFR in populations with HbA1c ≥6.0% and HbA1c <6.0%. Distributions of estimated GFR are shown separately for diabetic individuals (defined as HbA1c ≥6.0%) and for individuals with HbA1c <6.0%. The population with diabetes is represented by the *black column*, and individuals with HbA1c <6.0% are represented by the *white column*. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ versus individuals with HbA1c <6.0%

screening in Okinawa, proteinuria (defined as a dipstick urinalysis result of 1+ or more) was a strong predictor of ESKD [16]. The rate of decline of GFR in individuals with proteinuria was more than twofold faster than that in individuals without proteinuria [17]. This may suggest that most of CKD stage 3 and half of Japanese stage 4 + 5 CKD patients without proteinuria may progress slowly to ESKD and may not even reach ESRD during their

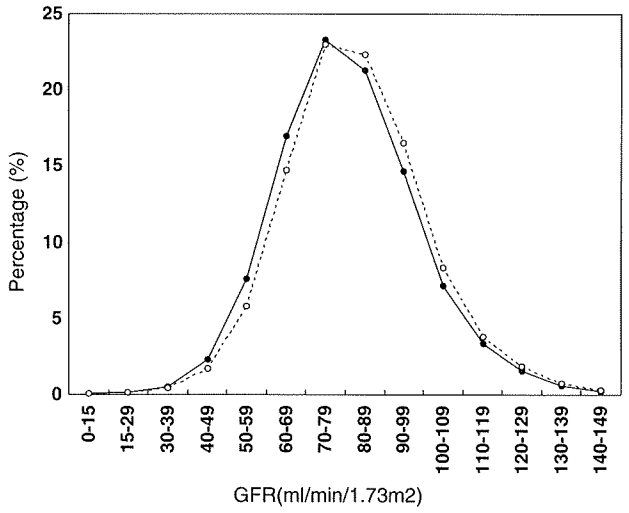

Fig. 6 Distribution of GFR in the Japanese general population. The distribution of estimated GFR for Japanese is shown by the *solid line*. We then recalculated the distribution of the GFR by age adjusting the Japanese population to the US population, as shown by the *dotted line*

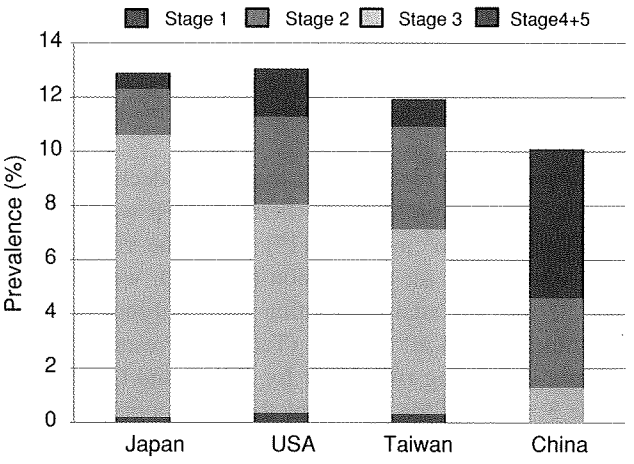

Fig. 7 Prevalences of CKD stages 1, 2, 3, and 4 + 5 in Japan, USA, Taiwan and China. The prevalence of each stage of CKD was obtained from previous publications. In Japan, the prevalence of CKD was estimated from accumulated data on 570,244 individuals aged 20 and over in the annual health check program in 2005. Proteinuria was evaluated by dipstick test, where 1+ and over was defined as proteinuria. In the USA, the prevalence of each stage of CKD was studied using data on nationally representative samples from 13,233 adults aged 20 and over taken from 1999 to 2004 [9]. The presence of albuminuria was estimated from the albumin-to-creatinine ratio, and microalbuminuria was defined as 30 mg/g creatinine. In Taiwan, the prevalence of each stage of CKD was estimated based on data from a private firm on 462,293 individuals aged 20 and over, obtained from 1994 to 2007 [13]. Proteinuria was evaluated by dipstick test, and (± or 1+) was defined as minimal proteinuria and (2+ and over) as overt proteinuria. In China, representative samples from 13,925 individuals aged 18 and older were analyzed [14]. Albuminuria was measured, and microalbuminuria was determined as ranging from 17 to 250 mg/g creatinine for males and from 25 to 355 mg/g creatinine for females