Risk Factors for Development of Decreased Kidney Function in a Southeast Asian Population: A 12-Year Cohort Study

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End-stage kidney disease has become an increasing burden in all regions of the world. However, limited epidemiologic data on chronic kidney disease in Southeast Asian populations are available. Therefore, a cohort study over a period of 12 yr (1985 to 1997) in 3499 employees of the Electric Generation Authority of Thailand, aged 35 to 55 yr, was conducted to determine the prevalence of decreased kidney function and risk factors associated with future development of decreased kidney function. The prevalence of decreased kidney function (GFR <60 ml/min) increased from 1.7% (95% confidence interval [CI], 1.3 to 2.1) in 1985 to 6.8% (95% CI, 5.7 to 7.9) in 1997, and the prevalence of elevated serum creatinine was 6.1% (95% CI, 5.3 to 6.9) and 16.9% (95% CI, 15.3 to 18.5) in 1985 and 1997 surveys, respectively. The adjusted odds ratio for future development of decreased kidney function was 2.57 (1.0 to 6.81) for systolic hypertension (>159 mmHg), 1.82 (1.12 to 2.98) for hyperuricemia (>6.29 mg/dl), 1.68 (1.02 to 2.77) for elevated body mass index (>24.9 kg/m^2) compared with subjects with systolic BP <140 mmHg, serum uric acid <4.5 mg/dl, and body mass index 20.8 to 22.8 kg/m^2. The rising prevalence of decreased kidney function in this population resulted mainly from the increasing prevalence of the risk factors in the population. Screening to detect decreased kidney function and early intervention to modify the associated risk factors should be considered in otherwise healthy individuals. Future studies are also necessary to determine whether implementation of these measures results in a reduction of ESRD incidence in the population.

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End-stage kidney disease has become an increasing burden in all regions of the world (1), including Southeast Asia. Identification of patients with early stages of renal impairment and those who are at risk for developing kidney diseases may offer an opportunity to alter the rising incidence of ESRD and associated cardiovascular deaths. In recognition to the importance of early detection, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative advisory board in the United States approved the development of clinical practice guidelines to define and to classify stages in the progression of chronic kidney disease (CKD) (2). The application of the Modification of Diet in Renal Disease (MDRD) formula for the estimation of GFR to data from the third National Health and Nutrition Examination Survey (NHANES III) has enabled investigators to provide an estimated prevalence of patients with decreased GFR among the US population (3).

Studies to determine the actual incidence and prevalence of individuals with kidney diseases in Southeast Asian populations, especially in Thai populations, are very limited and confined mostly to patients with ESRD (4). The incidence and progression of kidney disease may vary substantially between different populations. Studies from Singapore (5,6) indicated that the epidemiologic features of kidney diseases and associated risk factors might differ from those found in white populations and might also vary among Southeast Asian populations with different racial backgrounds. Determination of the epidemiologic features and identification of associated risk factors, especially any novel risk factors that may be unique for these populations, are mandatory.

The Electricity Generating Authority of Thailand (EGAT) study was originally designed in 1985 as a cross-sectional study of cardiovascular risk factors among EGAT employees (7). In 1997, the same individuals were resurveyed. The two surveys provided an opportunity to determine for the first time the prevalence of individuals with decreased kidney function as well as risk factors associated with the future development of decreased kidney function in a Southeast Asian population. The findings of this study should assist in deciding on specific prevention approaches and will be a guide for setting up national health prevention programs for kidney diseases.

Materials and Methods

Detailed methods of the EGAT Study are described elsewhere (7). The methods are provided here again in brief as well as additional, related information.

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Participants

In 1985, all employees of EGAT who were based at the company's main plant in Nonthaburi, Thailand, and were aged 35 to 54 yr were invited to participate in a survey of vascular risk factors. Of the 7824 individuals who were potentially eligible for inclusion in the study in 1985, 3499 (2702 men and 797 women) volunteered to take part. All participants completed a self-administered questionnaire; underwent a physical examination; and provided laboratory investigations, including fasting blood samples after a 12-h overnight fast, a dipstick urinalysis for urinary protein, and an oral glucose tolerance test.

In 1997, 12 yr later, survival status was determined for 3318 (95%) participants, and 2967 (85%) of the study participants were resurveyed using procedures similar to those used in the 1985 survey. The study was approved by the Ramathibodi Hospital medical Ethical Committee and the EGAT. Written informed consent for each participant was obtained.

Determination of Renal Function

Serum creatinine (SCr) was performed by means of modified kinetic Jaffe reaction (8) by the same laboratory in both surveys. Coefficients of variation for creatinine determination during our study were 4.96% at 1.29 mg/dl and 5.23% at 4.0 mg/dl SCr, and stable quality control was maintained. For determining any drift in SCr measurements over the 12 yr, the medians of SCr for participants with age between 47 to 54 yr and without hypertension, diabetes, and proteinuria in the 1985 and the 1997 surveys were determined. This age range was selected because it was the only age range that was common to both surveys. The medians of SCr were 1.21 mg/dl for men and 0.97 mg/dl for women in the 1985 survey but 1.20 mg/dl for men and 0.91 mg/dl for women in the 1997 survey. There was no significant difference in the median of SCr in both genders, indicating no significant drift in SCr measurements over the 12 yr.

Because the MDRD study used SCr obtained from the Cleveland Clinic Laboratory and the measurement of SCr can vary across different laboratories, SCr was calibrated by using a two-step process as previously published (9). First, NHANES III creatinine values were calibrated to the Cleveland Clinic Laboratory, requiring a correction factor of 0.23 mg/dl (10). The mean creatinine values from our study, by gender-specific age groups, were aligned with corresponding corrected NHANES III gender-specific and age group mean SCr (11). The adjusted SCr then was used to determine estimated GFR according to the MDRD formula.

GFR was estimated from adjusted SCr using the simplified equation developed using data from the MDRD Study (12) as follows:

$$\text{GFR(ml/min per 1.73 m}^2\text{)} = 186.3 \times (\text{SCr})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women})$$

Participants with decreased kidney function were defined primarily by the presence of GFR <60 ml/min per 1.73 m^2 using the modified MDRD formula. Patients with decreased kidney function were classified further according to the Kidney Disease Outcomes Quality Initiative classification of CKD (2) as follows: GFR (ml/min per 1.73 m^2) 30 to 59 for stage 3, 15 to 29 for stage 4, and <15 for stage 5.

As the MDRD formula includes an adjustment for age, the estimated GFR in this cohort from the second survey might be decreased as a result of more advanced age in this cohort and might result in an artificial elevation in CKD prevalence. A subsequent analysis was performed on the basis of only SCr. Participants with unadjusted SCr greater than the upper normal limit values, derived from the upper 95th percentile of SCr from participants aged between 35 and 45 yr, without hypertension, diabetes, or proteinuria, were defined as having elevated SCr. The cutoff values for normal SCr are 1.49 mg/dl for men (n = 1491) and 1.13 mg/dl for women (n = 565).

Definitions

The results of the dipstick urinalysis (Labstix; Bayer Corp., Pymble, Australia) were interpreted by well-trained medical personnel and were recorded as (−), (±), (1+), (2+), (3+), and (4+). Urine dipstick protein levels of (−) or (±) were regarded as normal, whereas proteinuria 1+ or above was recorded as proteinuria. Systolic hypertension was defined as systolic BP 140 mmHg or more and was classified according to modified criteria as described by the the Sixth Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP (JNC-6) (13). Diastolic hypertension was defined as diastolic BP 90 mmHg or more. Diabetes was defined as previously reported (7).

Subgroup Analysis

To determine whether an alteration in the prevalence of decreased kidney function in the 1997 survey was not merely a result of increasing age among this cohort, we performed a subgroup analysis among participants aged 47 to 54 yr in the 1985 survey and in participants with the same age range in the 1997 survey. This age range was selected because it was the only age range that was common to both surveys.

Statistical Analyses

Data are presented as mean ± SD for continuous variables and as proportions for categorical variables. $P < 0.05$ was considered statistically significant. A paired or an unpaired t test, as appropriate, was applied for a comparison of group means, and a χ^2 test was applied for proportions. Continuous variables, including age, body mass index (BMI), serum cholesterol, and serum uric acid, were divided into quartiles, but the severity of hypertension was classified according to modified JNC-6 criteria (13).

The primary outcome of interest was the development of decreased kidney function. Participants who had normal kidney function in 1985 and subsequently developed decreased kidney function in 1997 were identified. The odds ratios for risk factors associated with future development of decreased kidney function over the 12-yr follow-up were calculated from all participants with normal kidney function in the 1985 survey. The unadjusted odds ratios between the exposure variables and the future development of decreased kidney function were determined by univariate logistic regression analysis. A multivariate logistic regression analysis then was performed to evaluate the simultaneous effects of the various exposure variables, with adjustment for any confounding variables. The exposure variables, including BMI, systolic and diastolic BP, diabetes, proteinuria, serum uric acid, serum cholesterol, and history of smoking, had been assessed in the 1985 survey. Age and gender were not included in the logistic analyses because of the presence of both variables in the MRDR formula used for the calculation of GFR. To confirm the findings from the initial multivariate logistic analysis and to determine whether age was also an independent risk factor associated with the development of decreased kidney function, we determined the association between the aforementioned exposure variables and the development of elevated SCr (>1.49 mg/dl in men and >1.13 in women) by using the same analytical method, but age was also added in the exposure variables for this subsequent analysis. All statistical analyses were performed using SPSS software (SPSS Version 10; SPSS Inc., Chicago, IL).

Results

During the interval between both surveys, 367 participants were lost to follow-up and 165 participants died. Characteristics of the populations in both the 1985 and the 1997 surveys are shown in Table 1. The characteristics, determined in 1985 survey, of those who participated in both surveys are also presented in Table 1. There was no significant difference in the characteristics of those who participated only in the 1985 survey and those of individuals who participated in both surveys. The mean age, prevalence of both systolic and diastolic hypertension, diabetes, and proteinuria were higher in the 1997 survey. BMI, systolic BP, diastolic BP, and serum cholesterol of participants in 1997 survey also increased. By contrast, the prevalence of smokers declined by nearly twofold.

The percentages of participants with decreased kidney function increased from 1.7% (1.3 to 2.1%) in the 1985 to 6.8% (5.7 to 7.9%) in the 1997 surveys, based on the adjusted SCr ($P < 0.05$). The prevalence of CKD stage 3, stage 4, and stage 5 was 1.6, 0.1, and 0% for the 1985 survey and 6.4, 0.2, and 0.2% for the 1997 survey, respectively. In the 1997 survey, 530, 8, and 6 participants had developed new CKD stages 3, 4, and 5, respectively. The estimated incidence for CKD stages 3, 4, and 5 over the 12-yr follow-up was, respectively, 5215, 113, and 150 per million population per year. The prevalence of elevated SCr also increased from 6.1% (95% confidence interval [CI], 5.3 to 6.9) in the 1985 survey to 16.9% (95% CI, 15.3 to 18.5) in the 1997 survey ($P < 0.05$).

The overall prevalence of proteinuria was 2.64 and 6.10% of the participants in the 1985 and the 1997 surveys, respectively ($P < 0.05$). The prevalence of proteinuria in the 1985 survey was significantly higher in participants with than without decreased kidney function (8.6 *versus* 2.5%; $P < 0.05$), and the prevalence was also more common in participants with hypertension (8.9%) and diabetes (7.4%).

Risk Factors for Future Development of Decreased Kidney Function

The unadjusted and adjusted odds ratios for risk factors associated with the future development of decreased kidney function, based on adjusted SCr, over the 12-yr follow-up are shown in Table 2. Systolic BP (>159 mmHg), serum uric acid level (>6.3 mg/dl), and BMI (>24.9 kg/m^2) were found to be independent risk factors associated with the future development of decreased kidney function.

The subsequent analyses for the association between the exposure variables, including age, and the development of elevated SCr also confirmed that systolic BP and serum uric acid were independent risk factors for the development of decreased kidney function. In addition, total cholesterol (≥248.4 mg/dl) was a risk factor for the development of elevated SCr, but age was not an independent risk factor for the development of decreased kidney function (Table 3).

Subgroup Analysis in Participants Aged 47 to 54 Years

Characteristics for participants aged 47 to 54 yr in both surveys are shown in Table 4. Although the adjusted SCr in both surveys was comparable, 0.92 ± 0.19 mg/dl for the 1985 survey and 0.89 ± 0.51 mg/dl for the 1997 survey, there was a small but significant elevation in the prevalence of decreased kidney function among participants aged 47 to 54 yr ($P < 0.05$). The overall prevalence of CKD increased from 2.6% (95% CI, 1.7 to 3.9) and 2.8% (95% CI 1.8 to 4.2) for men and 1.5% (95% CI, 0.2 to 5.4) for women in the 1985 survey to 4.5% (95% CI, 3.4 to 5.8) and 3.4% (95% CI, 2.3 to 4.9) for men and 6.8% (95% CI, 4.5 to 9.8) for women in the 1997 survey. The prevalence of participants with systolic and diastolic hypertension, means of systolic and diastolic BP, age, BMI, and serum cholesterol increased significantly in the 1997 survey compared with those in the 1985 survey (Table 4). However, the prevalence of diabetes

Table 1. Characteristics of participants in both surveys

Variable	1985 Survey		1997 Survey
	Complete 12-Yr Follow-Up[b]	Total 1985 Survey	
No of participants	2967	3499	2967
Age (yr)	42.50 ± 4.84	43.01 ± 5.10	54.92 ± 5.11[c]
Male gender (%)	75.9	77.2	75.9
BMI (kg/m^2)[a]	23.05 ± 3.07	23.08 ± 3.14	24.69 ± 3.40[c]
Smoker (%)	41.70	43.34	22.40[c]
Diabetic patients (%)	5.67	6.80	16.20[c]
Patient with proteinuria (%)	2.37	2.64	6.10
Systolic BP (mmHg)	120.1 ± 15.5	120.8 ± 16.3	135.9 ± 21.5[c]
Diastolic BP (mmHg)	74.9 ± 10.8	75.3 ± 11.1	81.6 ± 13.2[c]
Uric acid (mg/dl)	5.42 ± 1.34	5.43 ± 1.4	NA
Serum creatinine (mg/dl)	1.15 ± 0.10	1.16 ± 0.22	1.16 ± 0.49
Serum cholesterol (mg/dl)	222.8 ± 42.5	222.4 ± 43.2	238.6 ± 40.9[c]

[a]BMI, body mass index; NA, not available.
[b]The characteristics were determined in the 1985 survey.
[c]$P < 0.05$ *versus* participants in the 1985 survey.

Table 2. Unadjusted and adjusted odds ratios for the future development of decreased kidney function found in the 1997 survey[a]

Input Variable	Odds Ratio (95% CI)	
	Unadjusted	Adjusted
Systolic BP		
<140	1	1
140 to 159	1.38 (0.84 to 2.26)	1.01 (0.56 to 1.81)
>159	3.37 (1.60 to 7.09)[b]	2.57 (1.0 to 6.81)[b]
Diastolic BP		
<90	1	1
91 to 110	1.83 (1.11 to 3.02)[b]	1.34 (0.74 to 2.40)
>110	1.89 (0.89 to 4.03)	0.81 (0.29 to 2.21)
Presence of diabetes	1.98 (1.10 to 3.55)[b]	1.74 (0.95 to 3.19)
Presence of proteinuria	0.58 (0.23 to 1.50)	1.42 (0.53 to 3.77)
Serum uric acid (mg/dl)		
first quartile (1.50 to 4.49)	1	1
second quartile (4.50 to 5.39)	0.99 (0.59 to 1.67)	0.89 (0.52 to 1.53)
third quartile (5.40 to 6.29)	1.24 (0.76 to 2.04)	1.10 (0.65 to 1.84)
fourth quartile (6.30 to 14.50)	2.31 (1.45 to 3.66)[b]	1.82 (1.12 to 2.98)[b]
Serum cholesterol (mg/dl)		
first quartile (93.8 to 193.4)	1	1
second quartile (193.5 to 219.3)	1.01 (0.61 to 1.67)	0.95 (0.56 to 1.58)
third quartile (219.4 to 248.3)	1.21 (0.74 to 1.98)	1.11 (0.67 to 1.83)
fourth quartile (248.4 to 455.2)	1.46 (0.91 to 2.34)	1.23 (0.75 to 2.01)
BMI (kg/m^2)		
first quartile (14.55 to 20.86)	0.85 (0.48 to 1.48)	0.93 (0.53 to 1.64)
second quartile (20.87 to 22.81)	1	1
third quartile (22.82 to 24.92)	1.67 (1.03 to 2.72)[b]	1.51 (0.92 to 2.46)
fourth quartile (24.93 to 40.26)	2.13 (1.32 to 3.43)[b]	1.68 (1.02 to 2.77)[b]
Smoker	1.03 (0.73 to 1.45)	1.00 (0.70 to 1.45)

[a]The input variables were obtained from the 1985 survey. CI, confidence interval.
[b]$P < 0.05$.

in both surveys was not different and the percentage of male participants was lower in the 1997 survey.

Discussion

On the basis of the two surveys conducted in 1985 and in 1997, we have examined the kidney function in a cohort of EGAT employees. To our knowledge, this is among the first studies to estimate the prevalence of patients with decreased kidney function in a Southeast Asian population. On the basis of multivariate analysis of factors in patients with initially normal kidney function in 1985, this study identified systolic hypertension, hyperuricemia, and high BMI as independent predictors of the development of decreased kidney function after 12 yr of follow-up.

The prevalence of patients with GFR <60 ml/min per 1.73 m^2 in our study was 1.7% in 1985 and 6.8% in 1997, with most patients in CKD stage 3. It is unfortunate that there are no data on the prevalence of CKD from other Southeast Asian populations for comparison. Most studies on the prevalence of early stages of decreased renal function had come from white populations and vary considerably between studies. For example, the prevalence of CKD stage 3 was 0.8% among Americans aged between 40 and 50 yr in the NHANES III survey, when renal function was estimated by MDRD formula (3). The prevalence was 2.5% among Australian adults aged between 45 to 65 yr and 54.8% for ages above 65 yr, when renal function was estimated by using Cockcroft-Gault formula (14). The prevalence of impaired renal function varied from 0.22 to 8% when the classification of renal function was based on SCr (11,15–17). The variation may depend on patient characteristics, especially age, associated risk factors, and methods for the estimation of GFR, or the definition of impaired renal function. The incidence of CKD stage 5 or ESRD in our study was lower than the incidence of ESRD from registries of the United States, Taiwan, and Singapore. However, this estimate was based on only a few cases, which may be associated with considerable sampling error and cannot be extrapolated to the population as a whole. Moreover, the incidence of ESRD is dependent on access to or being offered renal replacement therapy. Thus, we cannot make a conclusive statement on the incidence of CKD stage 5 in Thailand.

In this study, the simplified MDRD 2 formula was preferred

Table 3. Unadjusted and adjusted odds ratios for future development of elevated creatinine (from the 1997 survey)[a]

Input Variable	Odds Ratio (95% CI)	
	Unadjusted	Adjusted
Systolic BP		
<140	1	1
140 to 159	1.29 (0.90 to 1.85)	1.06 (0.70 to 1.61)
>159	2.78 (1.51 to 5.12)[b]	2.49 (1.15 to 5.40)[b]
Diastolic BP		
<90	1	1
91 to 110	1.67 (1.15 to 2.43)[b]	1.29 (0.84 to 1.97)
>110	1.54 (0.86 to 2.77)	0.76 (0.36 to 1.64)
Presence of diabetes	0.99 (0.59 to 1.66)	0.87 (0.51 to 1.47)
Presence of proteinuria	1.24 (0.57 to 2.70)	1.17 (0.53 to 2.60)
Serum uric acid (mg/dl)		
first quartile (1.50 to 4.49)	1	1
second quartile (4.50 to 5.39)	1.27 (0.90 to 1.79)	1.20 (0.85 to 1.70)
third quartile (5.40 to 6.29)	1.47 (1.05 to 2.05)[b]	1.30 (0.92 to 1.84)
fourth quartile (6.30 to 14.50)	2.09 (1.49 to 2.92)[b]	1.75 (1.23 to 2.51)[b]
Serum cholesterol (mg/dl)		
first quartile (93.8 to 193.4)	1	1
second quartile (193.5 to 219.3)	1.36 (0.96 to 1.91)	1.30 (0.92 to 1.84)
third quartile (219.4 to 248.3)	1.30 (0.91 to 1.84)	1.22 (0.86 to 1.75)
fourth quartile (248.4 to 455.2)	1.68 (1.20 to 2.36)[b]	1.51 (1.06 to 2.13)[b]
BMI (kg/m^2)		
first quartile (14.55 to 20.86)	0.72 (0.51 to 1.02)	0.79 (0.56 to 1.13)
second quartile (20.87 to 22.81)	1	1
third quartile (22.82 to 24.92)	1.27 (0.93 to 1.75)	1.15 (0.83 to 1.59)
fourth quartile (24.93 to 40.26)	1.33 (0.96 to 1.85)	1.09 (0.78 to 1.54)
Age (yr)		
first quartile (35.00 to 38.99)	1	1
second quartile (39.00 to 41.99)	1.21 (0.86 to 1.70)	1.11 (0.78 to 1.56)
third quartile (42.00 to 46.99)	1.38 (1.02 to 1.85)[b]	1.26 (0.93 to 1.70)
fourth quartile (47.00 to 54.00)	1.51 (1.07 to 2.13)[b]	1.27 (0.89 to 1.81)
Smoker	1.03 (0.81 to 1.31)	0.97 (0.76 to 1.24)

[a]The input variables were obtained from the 1985 survey.
[b]$P < 0.05$.

to the MDRD 1 formula because serum albumin and blood urea nitrogen measurement were not available and the MDRD 2 formula loses very little predictive ability when compared with MDRD 1 (18). There are several limitations to the use of MDRD formula in estimating GFR. First, MDRD formulas were derived in patients with moderate to severe CKD but not in community-based samples with relatively good renal function. Second, the MDRD formula relies on the SCr measurements obtained from Cleveland Clinic Laboratories. Differences in measurements of SCr between laboratories can be significant (10,19). Calibration of creatinine measurement to the creatinine obtained from MDRD laboratories is necessary to avoid erroneous estimation of the prevalence of CKD (10). We performed an indirect calibration of SCr by using a similar method to the recently published study from the Framingham group of investigators (9). This calibration method is based on the assumption that the mean SCr among Thai individuals without hypertension and diabetes is the same as US individuals of the same age and gender. Third, the MDRD formula was derived mostly from white or black US individuals, but to our knowledge, it has not been validated in Asian populations. Race has been shown to have important effects on creatinine production and

Table 4. Characteristics of participants aged 47 to 54 years in the 1985 and in the 1997 surveys

Variables	1985 Survey	1997 Survey
No. of participants	952	1774
Age (yr)	49.76 ± 2.32	50.70 ± 2.13[a]
Male gender (%)	86.3	73.0[a]
BMI (kg/m^2)	23.67 ± 3.23	24.60 ± 3.38[a]
Patients with BMI >24.92 (%)	31.2	42.1[a]
Systolic BP	124.71 ± 17.85	132.34 ± 20.10[a]
Patients with systolic hypertension >159 (%)	6.3	9.8[a]
Diastolic BP	78.26 ± 11.17	80.80 ± 12.92[a]
Patients with diastolic hypertension >110 (%)	0.1	2.0[a]
Serum cholesterol (mg/dl)	223.2 ± 47.5	238.6 ± 41.7[a]
Patient with proteinuria (%)	3.50	6.70[a]
Diabetic patients (%)	11.10	12.60

[a]$P < 0.05$ *versus* participants in the 1985 survey.

tubular secretion (19). Despite these limitations, the MDRD formula represents the best available option for the estimation of GFR in large studies and provides an opportunity for comparison between studies and between different time points in a cohort study such as this one.

The MDRD formula is still of value in identifying new patients who developed a decline in GFR and identifying risk factors associated with the decline in the follow-up analysis of this cohort. By using multivariate logistic analysis, systolic hypertension (>159 mmHg), hyperuricemia (≥6.3 mg/dl), and elevated BMI (≥25 kg/m^2) were found to be independent risk factors associated with the development of new decreased kidney function. Systolic hypertension and hyperuricemia were confirmed by the subsequent analysis using elevated SCr as the output variable. In addition, the association between hypercholesterolemia and the development of elevated SCr was demonstrated. Age was not included in the analyses of independent risk factors associated with decreased renal function as a result of the presence of this factor in the MDRD formula. However, age was not an independent risk factor associated with the development of elevated SCr in our logistic models. The increasing prevalence of decreased kidney function in older individuals might result from an increase in age-related risk factors for the development of CKD.

There is significant controversy as to whether hypertension is a cause or a consequence of kidney diseases. Hypertension is a known risk factor for progression of kidney disease and development of ESRD (20). Previously, systolic BP was also shown to be highly predictive of ESRD in the Multiple Risk Factor Intervention Trial (MRFIT) cohort, whereas diastolic BP had a less important independent role (21). Recent community studies from the United States showed that hypertension was also independently associated with increased risk for developing new CKD (9,22). This study found that hypertension was the most important independent risk factor for future development of kidney disease in a Thai population.

Hyperuricemia has long been known to be associated with hypertension, vascular disease, and renal failure (23). However, whether hyperuricemia can directly cause renal impairment in humans remains controversial. Hyperuricemia was an independent risk factor for the progression of kidney disease in two studies on IgA nephropathy (24,25) but was not a predictor of decline in renal function in the MDRD study (26). In this study, hyperuricemia was an independent predictor of subsequent renal impairment. Hyperuricemia in our study was not a result of impaired renal function as all individuals who were included in the analysis had GFR ≥60 ml/min per 1.73 m^2 in the initial survey. The finding is supported by two epidemiologic studies from Japan (27,28). Further studies are necessary to confirm the risk for hyperuricemia in the development of decreased renal function.

High BMI or overweight is increasingly more prevalent in Thai populations. Severe obesity is known to cause glomerular disease (29). In the Framingham cohort, high BMI was an independent predictor of developing decreased kidney function (9). A community-based mass screening in Okinawa found that the cumulative incidence of ESRD increased by 1.5-fold for individuals in the highest quartile compared with those in the lowest quartile of BMI (30). In our study, elevated BMI (>25 kg/m^2) was shown to be an independent risk factor for the development of decreased kidney function. Although not significant, a similar trend also existed when impaired kidney function was defined by elevated SCr. Similarly, a follow-up of a cohort from the Physician's Health study also found that higher BMI predicted decreased GFR but not elevated creatinine (31). Compared with white populations, Asians develop increased cardiovascular complications at lower BMI and the upper limit of normal BMI is closer to 23 kg/m^2 rather than 25 kg/m^2 (32). An association between BMI >25 and the increased risk for proteinuria in a study from Singapore (5) is consistent with the notion that modest increases in BMI could be a risk factor for renal injury in an Asian population. Because of the inherent association among body weight, muscle mass, and SCr, more studies are necessary to understand better the relationship between obesity and kidney disease in Asians.

Hypercholesterolemia was found to be another risk factor for

the future development of impaired kidney function. The relative risk for the development of elevated SCr was 1.51 for serum total cholesterol ≥249 mg/dl. Elevated serum cholesterol has been shown to be correlated with faster progression of CKD (33). A meta-analysis of 12 controlled trials of lipid reduction also showed that cholesterol-lowing therapies had beneficial effect on the decline of GFR in patients with established CKD (34). Our findings support a recent prospective cohort study in men over 14 yr, in which a relative risk for elevated creatinine of 1.77 for total cholesterol >248.3 mg/dl was demonstrated (31) and a retrospective study in which severe hypercholesterolemia increases a risk for new renal disease by two- to fourfold (35). By contrast, serum cholesterol was not found to predict new-onset moderate CKD in the Framingham cohort (9). The conflicting evidence on the role of serum cholesterol level in predicting new kidney disease might result from differences in study designs and patient populations.

Diabetic nephropathy is a leading cause of ESRD in many countries, including Thailand (4). Results from population studies on the role of diabetes in the development of moderate decreased kidney function were less clear cut. Diabetes was found to be an independent predictor of new kidney disease in the Framingham cohort (9) and a cohort from Maryland (22). In the latter study, only patients with severe CKD were identified. By contrast, a cross-sectional survey from Australia found that diabetes was associated with proteinuria but not decreased GFR (14). Diabetes did not independently predict the development of moderately decreased GFR in another cohort of mostly white men from the Physician's Heath study (31) and was not associated with a decline in GFR in a Japanese cohort (36). We found that diabetes was associated with increased prevalence of proteinuria, a finding similar to previous studies from Singapore (5). Although diabetes was associated with increased risk for developing decreased renal function in this study, the increased risk was not statistically significant in the multivariate analysis. High mortality rate in diabetic individuals, many of whom might also have renal impairment, may lead to an underestimation of the role of diabetes in predicting decreased kidney function in this study.

The prevalence of proteinuria was 2.64% in the 1985 survey and was more prevalent in individuals with hypertension, decreased renal function, and diabetes. The prevalence of proteinuria in the community varies considerably between populations. The prevalence was 5.3% in a Japanese population (37) and was 1% in the NHANES III study of the US general population (38). For those with established renal disease, proteinuria is an important predictor of the risk of progression. However, the role of proteinuria to predict new-onset kidney disease remains to be established. Proteinuria was found to be an independent predictor of ESRD but not for CKD in a Japanese study (39). In our study, positive dipstick proteinuria was not associated with an increasing risk for future development of decreased kidney function. No obvious trend was seen, even when proteinuria was analyzed as a categorical variable (1+ to 4+; data not shown). The dipstick method is semiquantitative and may not represent 24-h urinary protein excretion. The limited number of individuals with proteinuria and normal renal function in 1985 might account for the failure to demonstrate an association between the presence of proteinuria and the risk for future development of decreased kidney function. Only 27 individuals had persistent proteinuria in both surveys. Additional analysis failed to demonstrate significant elevation in the risk for decreased renal function in this group of individuals. This may result partly from the insufficient number of individuals with persistent proteinuria.

The role of smoking as a risk factor for renal disease is being increasingly recognized. In a cross-sectional study from France, smoking was not associated with decreased creatinine clearance (40). By contrast, a cross-sectional study from Australia (41) found that smoking was independently associated with renal impairment and proteinuria. Data from prospective studies on the development of new CKD are also conflicting. Smoking was independently associated with new kidney disease in the Framingham study (9) and a cohort study from Washington University, MD (22) but not from the Physician's Health study (31). Data from Asia are limited. In a cohort from Japan, the number of cigarettes smoked correlated with the incidence of proteinuria, but cigarette smoking was not found to be an independent predictor of new proteinuria (42). In our study, smoking was not found to predict the development of decreased kidney function. Additional analysis was done to determine the effects of persistent smoking (reported smoking in both survey) and cessation of smoking (reported smoking only in the 1985 survey but no smoking in the 1997 survey). There was no significant difference in the relative risks of developing decreased renal function among individuals with persistent smoking (1.16; 95% CI, 0.26 to 5.16) and individuals with cessation of smoking (1.08; 95% CI, 0.69 to 1.69) when compared with individuals who had never smoked.

There was a significant increase in the prevalence of individuals with decreased kidney function in the 1997 survey. It was uncertain whether the increasing age of the individuals or an increase in age-related risk factors was the cause of rising prevalence. The subgroup analysis, limited individuals with age between 47 and 54 yr in both surveys, demonstrated that the prevalence of decreased kidney function in the subgroup still rose significantly in the 1997 survey but to a lesser extent. The prevalence of the risk factors for decreased kidney function, including hypertension, high BMI, and hypercholesterolemia, also increased significantly in the 1997 survey. Therefore, the alterations in the prevalence of the risk factors, rather than increase in age alone, should be the cause of the increasing prevalence in our population. This was confirmed when multiple logistic analysis was applied to determine the risk factors associated with elevation of SCr. Age was not an independent risk factor for developing elevated SCr. Although diabetes is currently a leading cause of renal failure in most geographic areas, the prevalence of diabetes among individuals aged 47 to 54 yr was not significantly different between the 1985 and the 1997 surveys. Therefore, an increasing prevalence of diabetes cannot account for the rising prevalence of decreased kidney function in this subgroup.

Some limitations in our study should be pointed out. First, in the 1997 survey, renal function was available from only 85% of

individuals who participated in the 1985 survey. Some individuals with decreased renal function might be lost to follow-up. This may lead to some bias in the estimation of incidence and risk factors for decreased renal function. Second, our studied population might not represent the general Thai population, the majority of whom are farmers. However, this selected cohort had the advantage of uniform access to health services and ease of follow-up. The extrapolation of findings from this study to other groups of the Thai population should be made with caution. Third, the cohort had only two surveys, 12 yr apart. The analyses were based mainly on the data obtained from the 1985 survey. The variability of the studied risk factors was uncertain over the 12-yr interval. Finally, it should be pointed out again that the calibration of SCr in this study was an indirect method as was done by Fox *et al.* (9). This study was neither a community-based survey nor a survey in the US population. The relationship between SCr and GFR also varies with race, and the MDRD formula has never been validated in a Thai population. However, the limitation should have little effect on the analysis for risk factors associated with developing decreased kidney function.

In conclusion, this is the first study to evaluate the prevalence of decreased kidney function in a Southeast Asian population. Systolic hypertension, hyperuricemia, elevated BMI, and hypercholesterolemia are associated with future development of impaired kidney function. The prevalence of decreased renal function and associated risk factors were elevated over the 12-yr follow-up. Screening to detect decreased kidney function and early intervention to modify the associated risk factors should be considered in otherwise healthy individuals. Future studies are also necessary to determine whether implementation of these measures results in a reduction of ESRD incidence in the population.

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