Risk Factors for Proteinuria in a Large, Multiracial, Southeast Asian Population

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Abstract. The factors associated with proteinuria were examined in a large multiracial Asian population participating in a screening program aimed at the early detection of renal disease. Of 213,873 adults who participated, 189,117 with complete data were included. Malay race, increasing age, both extremes of body mass index (BMI), self-reported family history of kidney disease (FKD), and higher systolic and diastolic BP measurements (even at levels classified as being within the normal range) were independently associated with dipstick-positive proteinuria. The odds ratios (OR) for proteinuria increased progressively with age. There was a J-shaped relationship between BMI and proteinuria (OR of 1.3, 1.00, 1.3, 1.6, and 2.5 for BMI of $\leq$18.00, 23.00 to 24.99, 25.00 to 27.49, 27.50 to 29.99, and $\geq$30.00 kg/m^2, respectively, compared with BMI of 18.01 to 22.99 kg/m^2). OR for proteinuria according to systolic and diastolic BP were significantly increased beginning at levels of 110 and 90 mmHg, respectively. In addition, the Malay race was associated with a significantly higher OR for proteinuria, compared with the Chinese race (OR of 1.3). Finally, FKD was significantly associated with proteinuria (OR of 1.7), whereas a family history of diabetes mellitus and a family history of hypertension were not. When family histories were analyzed by clustering, isolated FKD remained a significant determinant of proteinuria and the magnitude of the effect was not significantly different from that observed in the presence of a coexisting family history of diabetes mellitus or hypertension. This is the first study to evaluate factors associated with proteinuria in an Asian population. The epidemiologic study of renal disease in this population suggests that risk factors for renal disease might differ significantly among racial groups.

Proteinuria is a well recognized predictor of end-stage renal disease (ESRD) and all-cause mortality rates, as well as cardiovascular mortality rates (1–3). Recent studies suggest that low grades of proteinuria or microalbuminuria might be associated with early renal disease even in the nondiabetic population (3). Indeed, there has been increasing interest in the determination of risk factors for the development of proteinuria, because such studies might facilitate focused preventive and therapeutic efforts to delay the progression to significant renal damage (4).

Epidemiologic studies have suggested that markers for cardiovascular disease are also risk factors for renal disease and proteinuria (5,6). However, previous studies were limited by gender specificity (5) and by a relatively small number of subjects (6). In addition, those studies focused primarily on Caucasian populations. Extremely limited epidemiologic data are available in the literature for identification of risk factors for the development of urinary abnormalities among Asians, particularly among the Chinese population. Because Asians are at somewhat increased risk of developing ESRD and the epidemiologic features of their renal disease reflect a markedly different pattern, compared with that of Caucasians (7,8), it is conceivable that the associated risk factors for proteinuria and renal disease among Asians of varying racial backgrounds might be different. We sought to identify the determinants of proteinuria for Chinese, Malays, and Asian Indians in Singapore, a country reported by the United States Renal Data System as having the third highest ESRD incidence rate in the world (9). This study is based on a nationwide screening program that seeks to identify adults who are at increased risk for renal disease and hypertension.

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Materials and Methods

Study Population

This study is part of the ongoing Prevention Program of the National Kidney Foundation Singapore (NKFS), the largest charitable organization in the country, which provides subsidized dialysis care to >60% of the total ESRD population of the country (10). The Prevention Program, which was initiated in 1997, aims to reduce the inci-

dence of ESRD in Singapore via a comprehensive strategy of screening, early intervention, research, and improved care of individuals at risk for the development of renal disease. Screenings for urinary abnormalities and hypertension are major components of the program. The screening program targets four discrete populations, as follows: the working population (screening is performed at work sites), the general adult population (screening is performed at housing estates, at community centers, and through the use of mobile screening buses), the pediatric population (screening is performed at school sites), and the taxi driver population (an occupational cohort for which screening is performed at taxi repair offices). This study includes only data for the working population, for which screening was performed at work sites. Individuals who underwent screening through the community-based, school-based, and taxi driver-focused programs were excluded from these analyses because subjects from the community-based and taxi driver-focused programs were still being enrolled at the time of manuscript preparation. In addition, slight differences in methodology exist among the target populations. In particular, individuals who participate in the community-based program are subject to a nominal fee. Furthermore, in the work site screening program, the manner in which the subjects are invited to participate directly involves the employer. This raises the possibility that individuals who recognize that they have risk factors for chronic disease and exhibit urinary abnormalities might be less likely to participate in the work site screening program. To avoid the possibility of differences in participation rates among the various target populations, leading to selection bias, this analysis was limited to individuals who participated in the work site screening program.

Voluntary free health screening was offered to all companies in Singapore with a staff strength of >50 individuals, through each company's assigned coordinator (generally a member of the human resources department). The only additional NKFS requirement was the designation of a quiet 10- $\times$ 20-foot room, on the company premises, in which to conduct screening activities. The company coordinator circulated information regarding the health screening to all employees of the respective workplace. Interested employees signed up for screening on predetermined dates. Screening was conducted during an 8-h period each day. Health screening was performed by 16 teams composed of four staff nurses and three coordinators, all of whom were employees of the NKFS. Work site screening was performed on every working day of the year.

Of an estimated 5000 companies in Singapore with the minimal number of employees, 1700 (34%) participated in the program. A range of 20 to 95% of all employees in the screened companies took part in the screening exercise. A total of 213,873 subjects participated in the work site screening program during the period of January 1999 to December 2000. This period was selected because data on race were collected beginning in the year 1999. Of the total number of subjects who participated in the screening program, 19,542 women (9.1%) were excluded because they were undergoing menstruation at the time of the screening and 5214 subjects (2.4%) were excluded because of missing data. Complete information (except for family history data) was available for the 189,117 subjects included in the analyses.

In the analysis evaluating the association between a family history of kidney disease (FKD) and proteinuria, 30,291 subjects were excluded because of incomplete data on FKD, family history of diabetes mellitus (FDM), and family history of hypertension (FHTN). An additional 250 participants with known personal histories of hereditary renal disease (polycystic kidney disease) and/or family histories of hereditary kidney disease were excluded, leaving 158,576 subjects available for the analysis evaluating family histories of disease and proteinuria.

Screening Examinations

After providing consent, each subject completed a self-administered questionnaire regarding demographic information, medical history of renal disease, diabetes mellitus, or hypertension, FKD, FDM, and FHTN. The NKFS coordinator ensured completeness of the questionnaire responses. After removal of shoes and heavy clothing, each subject underwent weight and height measurements, using a calibrated scale. The body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in square meters). The subject was then asked to collect a clean-catch, midstream, random urine specimen, which was subjected to dipstick analysis (Labstix; Bayer Diagnostics, Tarrytown, NY) of protein, blood, and glucose according to the instructions provided by the dipstick manufacturer. After the subject rested for 5 min, BP was measured twice with an automated sphygmomanometer, according to previously published guidelines (11). An average of the two readings was calculated. A third measurement was performed with a mercury sphygmomanometer if the BP readings were $\geq$140 mmHg for systolic BP (SBP) or $\geq$90 mmHg for diastolic BP (DBP).

Because of poor discrimination between negative and trace-positive dipstick readings (12), abnormal urine screening results were defined as the presence of $\geq$1+ protein (equivalent to $\geq$30 mg/dl). Similarly, hematuria was defined as the presence of $\geq$1+ blood in dipstick analyses. BP abnormalities were defined according to Joint National Committee VI criteria (11). Briefly, stage 1 hypertension was defined as SBP of 140 to 159 mmHg or DBP of 90 to 99 mmHg, stage 2 hypertension as SBP of 160 to 179 mmHg or DBP of 100 to 109 mmHg, and stage 3 hypertension as SBP $\geq$ 180 mmHg or DBP $\geq$ 110 mmHg. Individuals who were identified as exhibiting urinalysis abnormalities or hypertension underwent on-site counseling with trained staff nurses. These nurses had undergone a 5-d training program that tested their ability to uniformly and appropriately apply the various screening tools, as well as establishing their competence in general health counseling. A detailed protocol outlining the standard examination and counseling procedures was provided for each screening nurse, to ensure consistency of the screening methods and counseling recommendations. In addition, semiannual meetings were conducted to reinforce and update the protocols. Random visits by senior nursing administrators were performed to ensure consistent practices by the screeners.

Each screening participant was given a written report of the screening results and the health counseling recommendations. Individuals who were identified as exhibiting abnormalities were instructed to pursue subsequent evaluations with their own physicians. Within 1 wk after completion of the screening, the nurses conducted follow-up calls to subjects with clinical abnormalities, to remind those individuals that further evaluation was necessary. During the study period, no follow-up information was available for the screening participants. All health-related information was made available only to the respective subject and was not directly available to the participating companies.

Data Handling

All survey forms and health screening results were entered into a database by a data management company (Masters Systems Inc., Singapore), using a double-entry system. Correlational analyses were performed to evaluate the consistency of the data entry process. Furthermore, each health screening form was scanned into a database by using proprietary software developed by the data entry company

Table 1. Characteristics of the study population (n = 189,117)[a]

Clinical Features	No. of Subjects
Gender	
male	100,397 (53.1%)
female	88,720 (46.9%)
Race	
Chinese	145,897 (77.1%)
Malay	19,921 (10.5%)
Indian	16,887 (8.9%)
other	6,412 (3.4%)
Age	
≤30 yr	70,368 (37.2%)
31 to 40 yr	56,772 (30.0%)
41 to 50 yr	39,545 (20.9%)
51 to 60 yr	16,410 (8.7%)
≥60 yr	6,022 (3.2%)
History of diabetes mellitus	
yes	3,893 (2.1%)
no	184,435 (97.5%)
unknown	789 (0.4%)
History of hypertension	
yes	12,529 (6.6%)
no	175,778 (92.9%)
unknown	810 (0.4%)
History of renal disease	
yes	3,143 (1.7%)
no	185,347 (98.0%)
unknown	627 (0.3%)
Smoking	
yes or in the past	34,583 (18.3%)
no	154,534 (81.7%)
BMI	
≤18.00 kg/m^2	9,821 (5.2%)
18.01 to 22.99 kg/m^2	85,958 (45.5%)
23.00 to 24.99 kg/m^2	37,047 (19.6%)
25.00 to 27.49 kg/m^2	30,633 (16.2%)
27.50 to 29.99 kg/m^2	14,894 (7.9%)
≥30.00 kg/m^2	10,764 (5.7%)
SBP	
≤109 mmHg	45,245 (23.9%)
110 to 129 mmHg	85,485 (45.2%)
130 to 139 mmHg	30,778 (16.3%)
140 to 159 mmHg	22,175 (11.7%)
160 to 179 mmHg	4,260 (2.3%)
180 to 199 mmHg	929 (0.5%)
≥200 mmHg	245 (0.1%)
DBP	
≤79 mmHg	116,979 (61.9%)
80 to 89 mmHg	50,608 (26.8%)
90 to 99 mmHg	16,778 (8.9%)
100 to 109 mmHg	3,995 (2.1%)
110 to 119 mmHg	645 (0.3%)
≥120 mmHg	112 (0.1%)
FDM[b]	
yes	31,505 (19.9%)
no	127,071 (80.1%)
FHTN[b]	
yes	37,775 (23.8%)
no	120,801 (76.2%)
FKD[b]	
yes	5,893 (3.7%)
no	152,683 (96.3%)
Cause of FKD[c]	
glomerulonephritis	25 (0.4%)
diabetes mellitus	332 (5.6%)
hypertension	212 (3.6%)
unknown	5,324 (90.3%)
Cluster of family histories[b]	
FDM + FHTN + FKD	1,626 (1.0%)
FDM + FHTN	14,270 (9.0%)
FDM + FKD	1,023 (0.6%)
FDM only	14,586 (9.2%)
FHTN + FKD	1,233 (0.8%)
FHTN only	20,646 (13.0%)
FKD only	2,011 (1.3%)
none	103,181 (65.1%)

[a] BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; FDM, family history of diabetes mellitus; FHTN, family history of hypertension; FKD, family history of kidney disease.
[b] In the subgroup with available family history data (n = 158,576).
[c] In the subgroup with FKD (n = 5,893).

(MasImage Document Retrieval System; Masters Systems). This allowed actual forms to be viewed on the computer screen. A final visual verification of every 33rd form was then performed by the NKFS Prevention Program database manager. Data entry error was noted to be only 0.2% of all variables entered into the database.

Statistical Analyses

The outcome under analysis was the presence of proteinuria, as defined by dipstick protein results of ≥1+. Exposure variables that were considered included gender, age, race, smoking, BMI, history of diabetes mellitus, hypertension, or renal disease, FDM, FHTN, FKD, SBP, and DBP. Categories of age were as follows: ≤30, 31 to 40, 41 to 50, 51 to 60, and ≥60 yr of age. BMI was classified as ≤18.00, 18.01 to 22.99, 23.00 to 24.99, 25.00 to 27.49, 27.50 to 29.99, or ≥30.00 kg/m^2. SBP was categorized as ≤109, 110 to 129, 130 to 139, 140 to 159, 160 to 179, 180 to 199, or ≥200 mmHg. DBP was categorized as ≤79, 80 to 89, 90 to 99, 100 to 109, 110 to 119, or ≥120 mmHg.

Data analyses and calculations were performed by using the SPSS statistical package, version 10.1 (SPSS Inc., Chicago, IL). The crude (unadjusted) relationships between the exposure variables and the presence or absence of proteinuria were examined in univariate logistic regression analyses. Multivariate logistic regression analysis was then performed to evaluate the simultaneous effects of the various exposure variables, with adjustment for the potential confounding effects of other factors. For this purpose, male, Chinese, ≤30 yr of age, nonsmoking status, no preexisting disease, BMI of 18.01 to 22.99 kg/m^2, SBP of ≤109 mmHg, and DBP of ≤79 mmHg were used as reference categories. Family histories of disease were treated as a cluster, to take into account possible additive effects of family histories of multiple diseases. Therefore, individuals were grouped into categories representing family histories of all three diseases (diabetes

Table 2. Frequency distribution of proteinuria and hematuria

	No. of Subjects
Proteinuria	
negative	187,103 (98.94%)
30 mg/dl (+)	1,518 (0.80%)
100 mg/dl (++)	410 (0.22%)
300 to 1000 mg/dl (+++/++++)	86 (0.05%)
Urinary abnormality	
isolated proteinuria	1,495 (0.79%)
isolated hematuria	17,139 (9.06%)
both hematuria and proteinuria	519 (0.27%)
none	169,971 (89.88%)

mellitus, hypertension, and kidney disease), family histories of a combination of any two of the three diseases, or a family history of only one of these diseases, using the absence of any family history as the reference category. Odds ratios (OR) and 95% confidence intervals were obtained for the final predictive model. Subgroup analysis according to race was performed for all except for the Asian Indian subgroup, because of the small number of Asian Indians with proteinuria ($n = 171$).

Results

Clinical and Demographic Findings Associated with Proteinuria

The clinical and demographic features of this work site screening population are presented in Table 1. Of the 189,117 participants included in this study, 53.1% (100,397 subjects) were male. Seventy-seven percent (145,897 subjects), 10.5% (19,921 subjects), 8.9% (16,887 subjects), and 3.4% (6412 subjects) represented Chinese, Malay, Asian Indian, and other racial groups, respectively. Only 2.1% (3893 subjects), 6.6% (12,529 subjects), and 1.7% (3143 subjects) of the study population had known histories of diabetes mellitus, hypertension, and renal disease, respectively. Eighteen percent had either current or previous exposure to smoking. The mean and median ages of the participants were 36.3 ± 11.3 and 34.0 yr, respectively. Eighty-eight percent of the subjects were ≤50 yr of age, consistent with the relative youth of the working population under study. BMI values between 18.01 and 22.99 kg/m^2, the range proposed as optimal for the Chinese population (13), were observed for 45.5% (85,958 subjects). SBP values in the range considered hypertensive (≥140 mmHg) (11) were observed for 14.6% (27,609 subjects). SBP values considered high normal (between 130 and 139 mmHg) were observed for an additional 16.3% (30,778 subjects). Eleven percent (21,530 subjects) demonstrated DBP measurements of ≥90 mmHg. An additional 26.8% (50,608 subjects) exhibited DBP readings between 80 and 89 mmHg.

Among subjects for whom complete family history data were available, FKD, FDM, or FHTN was present for 3.7% (5893 subjects), 19.9% (31,505 subjects), and 23.8% (37,775 subjects), respectively. When family histories of disease were clustered, 1.0% (1626 subjects) demonstrated family histories of all three diseases, 9.0% (14,270 subjects) had FDM and FHTN, 0.6% (1023 subjects) had FDM and FKD, 0.8% (1233 subjects) had FHTN and FKD, 1.3% (2011 subjects) had FKD alone, 9.2% (14,586 subjects) had FDM alone, and 13.0% (20,646 subjects) had FHTN alone; 65.1% (103,181 subjects) of the total study population had no family history of any of the three diseases.

The frequency distribution of dipstick proteinuria, as well as proteinuria with or without dipstick hematuria, is presented in Table 2. Proteinuria of ≥1+ was observed for 1.1% (2014 subjects) of this young adult working population. Among subjects with proteinuria of ≥1+, 0.79% (1495 subjects) of the total population exhibited isolated proteinuria and the remaining 0.27% (519 subjects) of the total population exhibited proteinuria with hematuria. Isolated hematuria, defined as dipstick hematuria of ≥1+, was observed for 9.06% (17,132 subjects) of the total population.

Table 3 presents the demographic and clinical characteristics that were associated with proteinuria in univariate analyses. Gender was not a significant predictor of the presence of proteinuria in this population. Malays were significantly more likely to exhibit proteinuria, with an OR of 1.6 ($P < 0.0001$), compared with Chinese subjects. Subjects with a history of diabetes mellitus, hypertension, or renal disease were significantly more likely to exhibit proteinuria in urinalyses, compared with those without a history of disease (OR of 5.9, 5.2, and 5.7, respectively; $P < 0.0001$ for all). Each increase in age category beyond 30 yr was observed to be associated with a progressively greater likelihood of proteinuria; individuals in the age categories of 31 to 40, 41 to 50, 51 to 60, and ≥61 yr demonstrated univariate OR of 1.4, 2.4, 3.4, and 7.9, respectively ($P < 0.0001$ for all), compared with individuals ≤30 yr of age. In addition, increasing BMI was significantly associated with proteinuria (OR of 1.2, 1.8, 2.5, and 4.3 for each increase in BMI category, compared with a BMI of 18.01 to 22.99; $P < 0.0001$ for all).

Both SBP and DBP were significantly associated with the presence of proteinuria (Table 3). Each progressive increase in SBP was associated with a progressively greater likelihood of proteinuria, even at SBP levels below the standard definitions for hypertension (11). Similarly, DBP increases above 79 mmHg, to levels not considered to be elevated, were significantly associated with the presence of proteinuria.

The presence of concomitant hematuria or glycosuria was significantly associated with proteinuria, with OR of 3.4 for subjects with associated hematuria and 3.6 for subjects with associated glycosuria ($P < 0.0001$). Finally, FKD and FHTN were associated with proteinuria, with OR of 2.5 ($P < 0.0001$) and 1.3 ($P < 0.0001$), respectively, whereas FDM was not a determinant of proteinuria (OR of 1.1, $P = 0.09$). In addition, when family histories of disease were analyzed by cluster, FKD (alone or in combination with FDM or FHTN) was associated with proteinuria. Because smoking status was not significantly associated with proteinuria in the crude analysis, it was excluded from further analysis.

Table 3. Univariate OR for the presence of proteinuria[a]

Clinical Feature	Univariate OR	95% CI	*P* Value
Gender (F/M)	0.9	0.8 to 1.0	0.074
Race (Chinese = ref)			
Indian	1.0	0.9 to 1.2	0.937
other	0.8	0.6 to 1.0	0.058
Malay	1.6	1.5 to 1.8	<0.0001
Age (≤30 yr = ref)			
31 to 40 yr	1.4	1.3 to 1.7	<0.0001
41 to 50 yr	2.4	2.2 to 2.7	<0.0001
51 to 60 yr	3.4	3.0 to 4.0	<0.0001
≥61 yr	7.9	6.8 to 9.2	<0.0001
Prior diabetes mellitus (yes *versus* no)	5.9	5.1 to 6.8	<0.0001
Prior hypertension (yes *versus* no)	5.2	4.8 to 5.8	<0.0001
Prior renal disease (yes *versus* no)	5.7	4.9 to 6.2	<0.0001
BMI			
≤18.0 kg/m^2	1.2	0.9 to 1.5	0.232
18.0 to 22.99 kg/m^2	ref	ref	ref
23.00 to 24.99 kg/m^2	1.2	1.2 to 1.6	<0.0001
25.00 to 27.49 kg/m^2	1.8	1.8 to 2.3	<0.0001
27.50 to 29.99 kg/m^2	2.5	2.5 to 3.3	<0.0001
≥30.00 kg/m^2	4.3	4.4 to 5.7	<0.0001
SBP (≤109 mmHg = ref)			
110 to 129 mmHg	1.4	1.2 to 1.6	<0.0001
130 to 139 mmHg	2.4	2.0 to 2.8	<0.0001
140 to 159 mmHg	4.6	3.9 to 5.3	<0.0001
160 to 179 mmHg	9.4	7.8 to 11.5	<0.0001
180 to 199 mmHg	18.1	13.9 to 23.6	<0.0001
≥200 mmHg	31.4	21.4 to 46.1	<0.0001
DBP (≤79 mmHg = ref)			
80 to 89 mmHg	1.9	1.7 to 2.1	<0.0001
90 to 99 mmHg	4.1	3.6 to 4.6	<0.0001
100 to 109 mmHg	6.5	5.5 to 7.7	<0.0001
110 to 119 mmHg	10.8	7.8 to 14.9	<0.0001
≥120 mmHg	42.2	26.7 to 66.7	<0.0001
Hematuria (yes *versus* no)	3.4	3.1 to 3.8	<0.0001
Glycosuria (yes *versus* no)	3.6	3.1 to 4.2	<0.0001
FDM[b] (yes *versus* no)	1.1	1.0 to 1.2	0.0908
FHTN[b] (yes *versus* no)	1.3	1.2 to 1.4	<0.0001
FKD[b] (yes *versus* no)	2.5	2.1 to 3.0	<0.0001
Cluster of family histories[b] (*versus* none)			
FDM + FHTN + FKD	2.0	1.4 to 2.8	0.0002
FDM + FHTN	1.2	1.0 to 1.4	0.0211
FDM + FKD	2.4	1.6 to 3.6	<0.0001
FHTN + FKD	3.0	2.2 to 4.2	<0.0001
FDM only	1.1	0.9 to 1.3	0.5031
FHTN only	1.3	1.2 to 1.5	<0.0001
FKD only	3.1	2.4 to 4.1	<0.0001
Smoking (yes *versus* no)	0.996	0.9 to 1.1	0.940

[a] OR, odds ratio; CI, confidence interval; ref, reference value.
[b] In the subgroup with available family history data.

Adjusted Analyses

The adjusted OR for the factors associated with proteinuria are presented in Table 4. Gender was not associated with proteinuria in the multivariate analysis. The Malay race remained significantly associated with proteinuria, with a 30% increase in the odds of exhibiting proteinuria ($P < 0.0001$), compared with the Chinese racial group. Increasing age was also associated with proteinuria, although OR were significant

Table 4. Multivariate OR for the presence of proteinuria[a]

Clinical Feature	Multivariate OR	95% CI	*P* Value
Gender (F/M)	1.0	0.9 to 1.1	0.858
Race (Chinese = ref)			
Indian	0.9	0.7 to 1.1	0.190
other	0.8	0.6 to 1.1	0.274
Malay	1.3	1.2 to 1.5	<0.0001
Age (≤30 yr = ref)			
31 to 40 yr	1.1	0.9 to 1.2	0.457
41 to 50 yr	1.2	1.0 to 1.4	0.010
51 to 60 yr	1.3	1.1 to 1.6	0.002
≥61 yr	2.7	2.2 to 3.3	<0.0001
Prior diabetes mellitus (yes *versus* no)	2.0	1.6 to 2.4	<0.0001
Prior hypertension (yes *versus* no)	1.8	1.6 to 2.0	<0.0001
Prior renal disease (yes *versus* no)	3.5	2.9 to 4.3	<0.0001
BMI			
≤18.00 kg/m^2	1.3	1.0 to 1.7	0.031
18.01 to 22.99 kg/m^2	ref	ref	ref
23.00 to 24.99 kg/m^2	1.0	0.9 to 1.2	0.628
25.00 to 27.49 kg/m^2	1.3	1.2 to 1.6	<0.0001
27.50 to 29.99 kg/m^2	1.6	1.3 to 1.9	<0.0001
≥30.00 kg/m^2	2.5	2.2 to 3.0	<0.0001
SBP (≤109 mmHg = ref)			
110 to 129 mmHg	1.2	1.0 to 1.4	0.046
130 to 139 mmHg	1.4	1.2 to 1.8	0.001
140 to 159 mmHg	1.7	1.4 to 2.2	<0.0001
160 to 179 mmHg	2.3	1.8 to 3.1	<0.0001
180 to 199 mmHg	3.3	2.3 to 4.8	<0.0001
≥200 mmHg	3.8	2.2 to 6.5	<0.0001
DBP (≤79 mmHg = ref)			
80 to 89 mmHg	1.1	1.0 to 1.3	0.148
90 to 99 mmHg	1.5	1.2 to 1.8	<0.0001
100 to 109 mmHg	1.7	1.3 to 2.1	<0.0001
110 to 119 mmHg	1.8	1.2 to 2.8	0.006
≥120 mmHg	4.5	2.4 to 8.5	<0.0001
Hematuria (yes *versus* no)	2.9	2.6 to 3.3	<0.0001
Glycosuria (yes *versus* no)	1.5	1.3 to 1.8	<0.0001
Cluster of family histories[b] (*versus* none)			
FDM + FHTN + FKD	1.3	0.9 to 1.8	0.225
FDM + FHTN	0.9	0.8 to 1.1	0.539
FDM + FKD	1.8	1.2 to 2.7	0.009
FHTN + FKD	1.9	1.4 to 2.8	<0.0001
FDM only	1.0	0.9 to 1.2	0.810
FHTN only	1.1	0.9 to 1.2	0.365
FKD only	2.0	1.5 to 2.6	<0.0001

[a] CI, confidence interval; ref, reference value.
[b] In the subgroup with available family history data.

only beyond 41 yr of age (OR of 1.2, 1.3, and 2.7 for age groups of 41 to 50, 51 to 60, and ≥61 yr, respectively, compared with the age group of ≤30 yr). The OR for proteinuria for six categories of BMI demonstrated a J-shaped pattern, such that the groups with BMI values of 18.00 to 22.99 and 23.00 to 24.99 kg/m^2 exhibited the lowest odds, whereas the lowest and highest BMI groups exhibited significantly greater odds for proteinuria. BMI values in the lowest category (≤18.00 kg/m^2) demonstrated an OR of 1.3 ($P = 0.031$). Higher BMI values were similarly associated with proteinuria (OR of 1.3 for BMI of 25.00 to 27.49 kg/m^2, 1.6 for BMI of 27.50 to 29.99 kg/m^2, and 2.5 for BMI of ≥30.00 kg/m^2; $P <$

0.0001 for all). Preexisting renal disease of unspecified cause was strongly associated with proteinuria (OR of 3.5, $P < 0.0001$). Histories of diabetes mellitus or hypertension persisted as significant determinants for proteinuria (OR of 2.0 and 18, respectively; $P < 0.0001$ for both).

SBP was associated with proteinuria, with a 40% increase in odds being noted even at SBP levels between 130 and 139 mmHg (OR of 1.4, $P = 0.001$). In addition, the association between SBP and proteinuria did not seem to have a minimal threshold level, because a trend for an increase in odds for proteinuria was observed even with SBP measurements between 110 and 129 mmHg (OR of 1.2, $P = 0.046$). The relationship between SBP and proteinuria was strong and graded, such that SBP categories of 140 to 159, 160 to 179, 180 to 199, and ≥200 mmHg were associated with OR of 1.7, 2.3, 3.3, and 3.8, respectively ($P < 0.0001$ for all). DBP was also independently associated with proteinuria. As was observed for SBP, DBP exhibited a strong graded relationship with proteinuria, without any clear threshold below which DBP did not have an effect. Each increase in DBP was associated with significantly greater odds of exhibiting proteinuria, beginning with DBP values of ≥80 mmHg (Table 4). Therefore, an individual with a DBP measurement between 80 and 89 mmHg would demonstrate an OR of 1.5 ($P < 0.0001$) for proteinuria, compared with an individual with a DBP measurement of ≤79 mmHg.

The presence of hematuria was associated with an almost threefold increase in the odds of exhibiting proteinuria (OR of 2.9, $P < 0.0001$). Finally, the presence of glycosuria was a significant determinant of proteinuria (OR of 1.5, $P < 0.0001$), even with adjustment for known diabetes mellitus. This finding suggests that a segment of the study population might have proteinuria and renal disease associated with previously undetected diabetes mellitus, as indicated by the presence of glycosuria. Supporting this hypothesis is the observation that, in a separate analysis that excluded subjects with a history of diabetes mellitus, the presence of glycosuria remained significantly associated with proteinuria (OR of 1.4, 95% confidence interval of 1.2 to 1.8, $P < 0.001$).

When family histories of disease were analyzed as a cluster, FKD alone remained significantly associated with proteinuria, with an OR of 2.0 ($P < 0.0001$), whereas FDM alone and FHTN alone were not significant determinants. The presence of both FKD and FHTN, as well as FKD and FDM, was also significantly associated with proteinuria (OR of 1.9 for FKD plus FHTN, $P < 0.0001$; OR of 1.8 for FKD plus FDM, $P = 0.009$). However, the presence of either isolated FDM or FHTN or a family history of all three conditions were not significantly associated with proteinuria.

Subgroup Analyses

To determine whether racial differences exist in factors associated with proteinuria, subgroup analyses were performed. As indicated in Table 5, increasing age, preexisting disease, BMI, SBP, DBP, FKD (either alone or in combination with FDM or FHTN), hematuria, and glycosuria were significantly associated with proteinuria for the Chinese racial group. For the Malay race, increasing age was less closely associated with proteinuria. In addition, only in the highest category was BMI associated with proteinuria among the Malays, in contrast to the Chinese, for whom the J-shaped relationship between BMI and the presence of proteinuria was retained.

Discussion

The major findings of this cross-sectional study are that increasing age, both extremes of BMI, and higher SBP and DBP measurements (even at levels still classified as being within the normal range) are associated with the presence of proteinuria. FKD alone, but neither FDM alone nor FHTN alone, was also significantly associated with proteinuria. Gender was not observed to be significantly associated with proteinuria in this Asian population. Finally, the Malay race was significantly associated with proteinuria, compared with the Chinese race. These findings persisted even after adjustment for the confounding effects of other variables, as well as preexisting diabetes mellitus, hypertension, or renal disease.

Age is a recognized risk factor for renal disease (14,15). This is attributed partly to glomerular obsolescence and decreased renal vascular flow (15). Our finding that age of ≥40 yr was significantly associated with proteinuria is consistent with published studies. The reason why age was observed to be significantly associated with proteinuria only among the Chinese and not among the Malays remains unclear and deserves further study. A potential explanation relates to the observation that Malays exhibit higher rates of cardiovascular risk factors and outcomes (16), and possibly associated renal disease or proteinuria, such that older, healthy, working Malays who might have undetected proteinuria might be underrepresented in this study, resulting in the so-called "competing risks" phenomenon (17).

The finding that elevated DBP and SBP are associated with proteinuria is not unexpected. Hypertensive nephrosclerosis is one of the leading causes of ESRD (8). Prospective studies, such as Multiple Risk Factor Intervention Trial (MRFIT), have provided evidence that hypertension leads to chronic renal damage, at least among men (5). In the latter study, the effect of elevated SBP or DBP on the subsequent development of ESRD was strong and graded and existed at BP levels classified as normal but not optimal. In another analysis of the MRFIT data, each 9-mmHg increase in DBP was associated with an OR of 1.37 for the presence of dipstick-positive proteinuria (2). In the only study evaluating the relationship between BP and ESRD in an Asian (Japanese) population, high DBP was associated with an OR of 1.4 for ESRD, compared with individuals with DBP of ≤69 mmHg (18). In a study of another population, an 18-mmHg increase in SBP was significantly associated with microalbuminuria (6). Plausible mechanisms have focused on the elevation in the pressure transmitted to the glomeruli, which might result in sclerosis and proteinuria with time (19).

Our study extends previously published findings by suggesting that the relationship between SBP or DBP elevations and renal damage is present even in the earlier stages of renal disease, as defined by the presence of proteinuria. This is

Table 5. Multivariate OR for the presence of proteinuria in subgroup analyses according to race[a]

Clinical Feature	Chinese			Malays		
	Multivariate OR	95% CI	*P* Value	Multivariate OR	95% CI	*P* Value
Gender (F/M)	1.0	0.9 to 1.1	0.999	1.2	0.9 to 1.5	0.204
Age (≤30 yr = ref)						
31 to 40 yr	1.2	1.0 to 1.4	0.084	0.7	0.5 to 1.0	0.065
41 to 50 yr	1.4	1.2 to 1.7	<0.0001	0.7	0.5 to 1.0	0.036
51 to 60 yr	1.7	1.4 to 2.0	<0.0001	0.6	0.4 to 1.0	0.033
≥61 yr	3.5	2.8 to 4.4	<0.0001	0.8	0.4 to 1.6	0.623
Prior diabetes mellitus (yes *versus* no)	1.9	1.5 to 2.5	<0.0001	2.7	1.7 to 4.3	<0.0001
Prior hypertension (yes *versus* no)	1.9	1.7 to 2.2	<0.0001	1.3	0.9 to 1.8	0.165
Prior renal disease (yes *versus* no)	3.5	2.8 to 4.3	<0.0001	4.6	2.6 to 1.8	0.165
BMI						
≤18.0 kg/m^2	1.4	1.1 to 1.9	0.017	0.7	0.5 to 2.2	0.537
18.01 to 22.99 kg/m^2	ref	ref	ref	ref	ref	ref
23.00 to 24.99 kg/m^2	1.1	0.9 to 1.3	0.464	0.8	0.5 to 1.3	0.400
25.00 to 27.49 kg/m^2	1.5	1.3 to 1.7	<0.0001	1.0	0.7 to 1.6	0.819
27.50 to 29.99 kg/m^2	1.7	1.4 to 2.0	<0.0001	1.4	0.9 to 2.1	0.133
≥30.00 kg/m^2	2.6	2.2 to 3.2	<0.0001	2.1	1.4 to 3.0	<0.0001
SBP (≤109 mmHg = ref)						
110 to 129 mmHg	1.1	0.9 to 1.3	0.368	1.5	0.9 to 2.4	0.121
130 to 139 mmHg	1.3	1.0 to 1.7	0.023	1.7	0.9 to 3.0	0.097
140 to 159 mmHg	1.4	1.1 to 1.8	0.010	3.3	1.8 to 6.1	<0.0001
160 to 179 mmHg	1.7	1.2 to 2.3	0.002	5.0	2.4 to 10.7	<0.0001
180 to 199 mmHg	2.4	1.6 to 3.8	<0.0001	9.7	3.7 to 25.7	<0.0001
≥200 mmHg	2.8	1.5 to 5.4	0.002	10.6	2.9 to 39.1	<0.0001
DBP (≤79 mmHg = ref)						
80 to 89 mmHg	1.1	0.9 to 1.3	0.386	1.3	0.9 to 1.9	0.163
90 to 99 mmHg	1.5	1.2 to 1.8	<0.0001	1.7	1.1 to 2.7	0.030
100 to 109 mmHg	1.6	1.2 to 2.2	0.002	1.8	1.0 to 3.3	0.875
110 to 119 mmHg	2.0	1.2 to 3.3	0.006	0.9	0.3 to 3.0	0.875
≥120 mmHg	3.4	1.5 to 7.9	0.005	11.3	2.9 to 44.0	<0.0001
Hematuria (yes *versus* no)	2.7	2.4 to 3.1	<0.0001	3.6	2.8 to 4.8	<0.0001
Glycosuria (yes *versus* no)	1.4	1.1 to 1.7	0.004	1.7	1.1 to 2.5	0.013
Cluster of family histories[b] (*versus* none)						
FDM + FHTN + FKD	1.3	0.9 to 2.0	0.204	1.0	0.4 to 2.5	0.969
FDM + FHTN	1.0	0.8 to 1.2	0.623	0.8	0.5 to 1.3	0.463
FDM + FKD	1.7	1.1 to 2.9	0.031	1.8	0.6 to 5.1	0.272
FHTN + FKD	1.6	1.0 to 2.4	0.029	3.3	1.5 to 7.3	0.004
FDM only	0.9	0.8 to 1.2	0.586	1.0	0.7 to 1.5	0.964
FHTN only	1.0	0.9 to 1.2	0.696	1.1	0.8 to 1.6	0.555
FKD only	1.9	1.4 to 2.6	<0.0001	2.7	1.1 to 6.2	0.023

[a] CI, confidence interval; ref, reference value.
[b] In the subgroup with available family history data.

consistent with observations that individuals with isolated borderline systolic hypertension are at significantly increased risk for cardiovascular outcomes (20), given recent observations that proteinuria and cardiovascular risk factors and outcomes are strongly associated with each other (21). The fact that even mild BP elevations were associated with proteinuria for this Asian population might suggest that normal BP values for Asians are not equivalent to those established for Caucasians. This might indicate the need to establish BP nomograms specific to the Asian population.

In our study, elevated BMI values were also significantly associated with proteinuria. For the Chinese racial group, each BMI category above 25 kg/m^2 was associated with progressively higher OR for the presence of proteinuria (Table 5). Among the Malays, the relationship between BMI and proteinuria was pronounced only at BMI levels of ≥30 kg/m^2. Chi-

nese generally exhibit lower mean BMI values, compared with other ethnic groups in Singapore (16). Indeed, it has been proposed that the upper limit of the normal BMI range for Chinese subjects is closer to 23 kg/m^2 (13). Therefore, the deleterious effects of elevated BMI values on the kidney (such as hyperfiltration and proteinuria), which are generally associated with severe obesity (22), could potentially occur at much lower BMI levels in the Chinese population. The observation that BMI values of $<$18.00 kg/m^2 were associated with proteinuria among the Chinese subjects suggests a different pathophysiologic process. It is possible that proteinuria and undetected renal disease in adults might lead to decreased weight gain and low BMI. Alternatively, individuals with low BMI values (and conceivably low birth weights) might be at higher risk for proteinuria and renal disease, consistent with previous studies that suggested that low birth weights and low renal masses lead to increased risks of hyperfiltration and renal damage during adulthood (23,24). Because this is a cross-sectional study, it is not possible to determine the sequence of events.

In our study, FKD alone, but neither FDM alone nor FHTN alone, was significantly associated with proteinuria. Although the odds for proteinuria associated with FKD (OR of 2.0) were independent of coexisting FDM and/or FHTN, clustering of FKD with either FDM (OR of 1.8) or FHTN (OR of 1.9) was also associated with a significant risk for proteinuria. It is notable, however, that FKD, but not FDM or FHTN (alone or in combination), was necessary and sufficient for an association with proteinuria. The coexistence of all three diseases (FDM plus FHTN plus FKD) was not significantly associated with proteinuria in our study (OR of 1.3). A potential explanation might be that individuals with family histories of all three conditions are more aware of their familial predisposition to chronic disease, such that they might have elected to avoid putative risk factors for proteinuria and renal disease, compared with individuals without family histories of all three diseases. Alternatively, individuals with family histories of all three conditions might be at increased risk for renal disease and proteinuria not because of the family history or genetic predisposition itself but rather because of the presence of associated determinants of diabetes mellitus and hypertension within families, such as elevated BMI. Therefore, FDM, FHTN, and FKD were indeed significant predictors of proteinuria in univariate analyses (OR of 2.0, $P = 0.0002$). However, with consideration of other possible explanatory variables (such as BMI), the association was no longer significant, as demonstrated in the multivariate analysis.

Studies of familial clustering of ESRD suggest that it is the family history of ESRD itself that confers an increased risk of developing ESRD, irrespective of the mechanism of renal injury. Freedman *et al.* (25) reported that, whereas eight of 50 patients (16%) with lupus nephritis had a first-, second-, or third-degree relative with ESRD, only one of the eight relatives with ESRD had lupus or a collagen vascular disease. A recent study of familial clustering of ESRD in a large incident cohort of dialysis patients in a wide geographic area in the southern United States confirmed earlier reports of the familial aggregation of ESRD attributable to hypertension and diabetes mellitus and revealed a genetic susceptibility to the development of ESRD attributable to glomerulonephritis and other causes of renal disease among both African Americans and Caucasians (26). However, the similar proportions of prevalent cases involving first- or second-degree relatives with ESRD in that study (22.2% for incident dialysis patients with diabetes mellitus, 18.9% for hypertension, and 22.7% for glomerulonephritis) suggest that there is an inherited susceptibility to progressive renal failure, independent of the cause of ESRD.

Finally, the Malay race was observed to be significantly associated with proteinuria (Table 4). This finding is consistent with observations that Malays exhibit the highest incidence rate of ESRD, compared with other racial groups in Singapore (262, 216, and 148 cases/million population among Malays, Chinese, and Asian Indians, respectively; adapted from reference 7). A similar relationship between the Malay race and proteinuria was observed among non-Chinese children in Singapore (24). Potential explanations that require further evaluation include racial differences in nutrition, socioeconomic status, or genetic predisposition. Differences in birth weights among these minority ethnic groups might also account for increased predisposition to both hypertension and renal disease (24).

Our study has several potential limitations that must be considered in the interpretation of our findings. As in any cross-sectional study, causation cannot be established because the sequence of events between exposure and outcome is not defined. For example, it is possible that individuals with undetected renal disease and proteinuria might present with mild elevations in SBP and DBP. However, our findings are consistent with other reports that mild BP elevations can lead to clinically significant renal disease (19). Information on potential confounding variables affecting the relationships between the various exposures analyzed and proteinuria was not available. In this regard, nutritional intake, cholesterol levels, fasting glucose levels, and other cardiovascular risk factors might have confounded the relationship between race and proteinuria. We are in the process of obtaining information on such potential confounders for a subset of our screening population. Another limitation of our study is that self-reported histories of disease were not confirmed by chart review or telephone interview. There is also the possibility of a selection bias, in that the individuals who volunteered to participate in the screening program might be more or less likely to manifest the relationships between BP, age, race, and proteinuria. The fact that our findings were strong, graded, and consistent with published reports suggests that bias is less likely. Another limitation of our study is the use of urine dipstick results as the outcome under consideration. Urine dipstick analysis is only a semiquantitative estimation of the severity of proteinuria. Errors in the classification of results are likely to be random (random misclassification), however, which tends to bias potential associations toward the null value (27). Therefore, our findings could reflect an underestimation of the true odds for proteinuria associated with age, race, BMI, BP, and FKD. Furthermore, in a study evaluating the relationship between random urine dip-

stick results and albumin/creatinine ratios, there was a 91% positive predictive value of ≥1+ proteinuria for both diabetic and nondiabetic populations (28). Dipstick-positive proteinuria was used as an outcome, as well as a predictor, in a study of the MRFIT population (2). Finally, the relative health and youth of our study population might limit the generalizability of some of our findings. In particular, the prevalence rates of proteinuria and elevated BP might not be representative of the total Singapore population. Therefore, the screening program was extended to involve community-based and taxi driver-focused screening. Data on these populations are still being collected. Despite the limited generalizability of our prevalence rates for proteinuria, we think that the associations we have reported will apply to other populations with the same racial background, particularly in Southeast Asia.

In conclusion, elevations in SBP and DBP (at levels considered acceptable) are associated with proteinuria in a multiracial Asian population. Other factors associated with proteinuria include age, BMI, and FKD. In addition, racial differences exist in the odds for proteinuria, as well as in the factors associated with proteinuria. This is the first study to evaluate factors associated with proteinuria in an Asian population. The epidemiologic study of renal disease in this population is of relevance because risk factors for renal damage might differ among non-Caucasians, as suggested by our study. The identification of factors associated with proteinuria might lead to the modification of putative risk factors for renal disease. This is of significance, because proteinuria and even microalbuminuria are associated with cardiovascular and renal outcomes, even in nondiabetic populations (19,29). Additionally, the determination of factors associated with proteinuria in this population could guide the design of a more focused screening strategy, by identifying individuals at higher risk for abnormalities. Such a targeted prevention strategy could potentially result in the reduction of ESRD in the population at highest risk for its development.

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