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ORIGINAL ARTICLE

Annual incidence of persistent proteinuria in the general population from Ibaraki annual urinalysis study

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Abstract
Background For a definitive diagnosis of chronic kidney disease, at least 2 consecutive positive results of proteinuria with an interval of >3 months are required. However, most previous reports were based on single-screening data.
Patients and methods The subjects in this study were participants in an annual health examination held in Ibaraki, Japan, between 1993 and 2003. The follow-up duration with serial urinalysis for 3 years of patients who were negative for proteinuria in the initial year was 330,614 person-years in males and 687,381 person-years in females among 81,854 male and 155,256 female subjects. We evaluated the incidence and risk factor for the incidence of proteinuria and persistent proteinuria.
Result The annual incidence of proteinuria and persistent proteinuria was 1.31 and 0.33 % in males and 0.68 and 0.14 % in females. Among the subjects without hypertension and diabetes, the annual incidence was 0.81 and 0.16 % in males and 0.37 and 0.06 % in females, respectively. Risk analysis indicated that hypertension in males [hazard ratio (HR) 2.052] and females (2.477), diabetes in males (3.532) and females (3.534) and reduced renal function in males (3.097) and females (2.827) were significant positive risks for development of persistent proteinuria.
Conclusion By annual urinalysis screening of the general population, 1 out of 303 male subjects and 1 out of 725 female subjects developed persistent proteinuria every year. Subjects with diabetes, hypertension and reduced renal function had a 2 or 3 times higher risk for the incidence of persistent proteinuria in both males and females.

Keywords Urinalysis · Chronic kidney disease · Persistent proteinuria · Risk factors

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Introduction

At present, it is considered that the worldwide population of patients with end-stage renal disease (ESRD) will continue to increase as a result of more patients requiring renal replacement therapy (RRT). Moreover, we know that chronic kidney disease (CKD) is a risk factor of not only progression to ESRD, but also the development of cardiovascular diseases (CVD) [1–3]. Therefore, we should promote reducing the incidence of CKD to save quality of life in the general population and economic loss due to the increasing number of ESRD patients.

In Japan, annual urinalysis screening programs were introduced for every schoolchild in 1973, for every working adult in 1972, and for residents >40 years of age in 1982 under the auspices of local governments and the Ministry of Health, Labor and Welfare of Japan [4]. However, Boulware et al. [5] reported that annual urinalysis screening for proteinuria is not cost-effective unless selectively directed toward a high-risk group such as older persons and persons with hypertension, or conducted at an infrequent interval. However, Kondo et al. [6] reported that

annual screening of proteinuria with dipsticks was cost-effective for the Japanese population. One reason for the opposite views on urinalysis screening comes from the difference in the prevalence of proteinuria among races [7–9]. In particular, the prevalence of proteinuria is high in the Japanese general population [4, 10] and in Asians generally [7]. Chronic glomerulonephritis (CGN) has been found to be a more frequent underlying renal disease for ESRD in Asians than in Caucasians [11, 12]. Most CGN patients have no symptoms at the early stage of the disease, and the only method for early detection is urinalysis [13]. The reduced number of new ESRD patients with CGN might be caused by early detection and early referral to nephrologists due to the annual urinalysis screening program in Japan [14, 15]. Proteinuria also accelerates a decline in the glomerular filtration rate (GFR) [16], and proteinuria is the strongest predictor of CKD stage progression [17].

Therefore, to explain the effectiveness of annual urinalysis screening, we had to elucidate the annual incidence of proteinuria and persistent proteinuria in the general population and focus on people without high risk of proteinuria such as hypertension and diabetes. To date, however, because most previous reports were based on single-screening data, we had no precise evidence of the incidence of persistent proteinuria for a period of more than 3 months, which is a required for a definitive diagnosis of CKD in the general population.

In this study, from the result of the annual health examination held in Ibaraki, Japan, we estimated the annual incidence of proteinuria and persistent proteinuria among the Japanese general population and among the population with or without diabetes, hypertension or reduced renal function. This analysis might provide clues for future screening policy for urinary abnormalities to reduce the number of CKD patients.

Subjects and methods

The participants in the annual health examination held in Ibaraki, Japan between 1993 and 2003 comprised 152,569 males and 267,594 females (age range 40–98 years (median 61 years). Among them, 63,728 males and 103,381 females did not receive serial urinalysis for 3 years, 5,174 males and 4,368 females had proteinuria at their initial urinalysis, and 1,813 males and 4,589 females had missing data. The prevalence of proteinuria in our subjects, i.e., a positive result for proteinuria in their first urine examination, was 3.4 % (5,174/152,569) in males and 1.6 % (4,368/267,594) in females. After we excluded those subjects, the study population comprised 81,854 male and 155,256 female subjects.

To diagnose persistent proteinuria, data obtained with an interval of >3 months is required by definition [18]. The incidence of persistent proteinuria in this study was defined as positive for proteinuria by consecutive annual urinalysis. The subjects were followed up until persistent proteinuria was recorded during the 10-year follow-up duration; their follow-up duration was 330,614 person-years in males and 687,381 person-years in females (Fig. 1).

We defined diabetes as subjects who were taking oral hypoglycemic or insulin treatment, subjects with fasting blood sugar ≥126 mg/dl or random blood sugar ≥200 mg/dl. Subjects having systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or taking anti-hypertensive medication were defined as hypertensive [19]. Estimated GFR (eGFR) was calculated from the simplified equation developed from the MDRD study [20] as follows: eGFR (ml/min/1.73 m^2) = 186.3 × (serum creatinine)$^{-1.154}$ × age$^{-0.203}$ × (0.742 for female subjects) without adjusting for Japanese covariant factors and we separated the subjects to normal renal function (eGFR ≥60 ml/min/1.73 m^2) and reduced renal function (eGFR <60 ml/min/1.73 m^2). These co-morbid conditions of the initial year were applied for the analysis.

Hypercholesterolemia was defined as total cholesterol (T-Cho) ≥220 mg/dl, low high-density lipoprotein cholesterol (HDL-C) as ≤35 mg/dl, and hypertriglyceridemia was defined as triglycerides (TG) ≥250 mg/dl.

Alcohol intake was defined as total alcohol consumption in grams per day calculated from questions on the number of glasses of wine, beer, fortified wines, sake, and liqueurs/

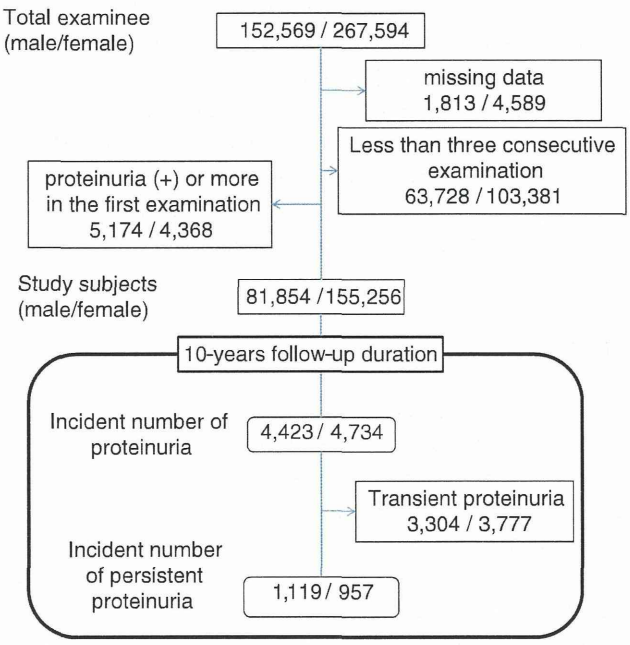

Fig. 1 Number of examinee and study subjects and their male:female ratio are shown

spirits per day. One glass of any alcoholic beverage was assumed to contain 10 g of alcohol. The total alcohol consumption was then classified into four categories—no alcohol consumption, occasional alcohol consumption, <20 g/day, and >20 g/day. Smoking habits were classified into three categories—non-smoker, previous smoker or current smoker.

Proteinuria was tested using dipstick (Ames Hemacombisticks; Bayer-Sankyo Ltd., Tokyo, Japan). A test result of '1+' or more was defined as positive. Serum creatinine concentration was measured by a modified Jaffe method (Creatinine-HR; Wako Pure Chemicals Industries, Ltd., Osaka, Japan) using an autoanalyzer (Hitachi 7350; Hitachi Ltd., Tokyo, Japan or RX-20; JEOL Ltd., Tokyo, Japan). Measurements of blood glucose, T-Cho, TG, and HDL-C were measured using an autoanalyzer (Hitachi 7350; Hitachi Ltd).

Statistical methods

To compare males and females and to compare subjects with presence and absence of hypertension, diabetes or reduced renal function, we applied the chi-squared test. The primary outcome for the analysis was the development of persistent proteinuria during the follow-up period. Variables were age, diabetes, hypertension and renal function (eGFR <60 ml/min), hypercholesterolemia (−, +), low HDL-C (−, +), hypertriglyceridemia (<150 mg/dl, 150−299 mg/dl, ≥300 mg/dl), obesity (−, +), cigarette smoking (never, previous smoker and current smoker with <1 pack/day and >1 pack/day), alcohol consumption (never, occasional drinker, alcohol consumption <20 g/day and alcohol consumption ≥20 g/day). Hazard ratios of proteinuria and persistent proteinuria development by sex were estimated by using Cox regression model after confirming the proportionality in each model (SAS software, version 8.3, SAS Institute Inc., CA, USA). A p value of <0.05 was considered statistically significant.

Result

Table 1 shows baseline characteristics of the study subjects. Male subjects were significantly older, more frequently with hypertension and diabetes, and less frequently with reduced renal function.

During the entire observation period, 4,423 male and 4,734 female subjects were newly positive for proteinuria and the annual incidence of proteinuria was 1.31 % in males and 0.689 % in females (Fig. 2a). Among them, 1,119 males and 957 females had continued to be positive for proteinuria. Consequently, the incidence of persistent proteinuria was 0.33 % in males and 0.14 % in females (Fig. 2a); 74.7 % (3,304/4,423) in males and 79.8 % (3,777/4,734) in females had transient proteinuria.

From the above results, 1 out of 303 male subjects and 1 out of 725 female subjects developed persistent proteinuria every year in our study subjects. The incidence of proteinuria and the incidence of persistent proteinuria were both significantly higher in males.

When separating the subjects by co-morbid conditions, the annual incidence of proteinuria among the subjects without hypertension and diabetes was 0.83 % in males and 0.37 % in females (Fig. 2b). Moreover, the annual incidence of persistent proteinuria was 0.16 and 0.06 %, respectively, and 1 out of 632 male subjects and 1 out of 1,626 female subjects developed persistent proteinuria every year.

The annual incidence of proteinuria and persistent proteinuria in the subjects with hypertension, diabetes or reduced renal function was significantly higher than the incidence without each condition. Meanwhile, the annual incidence of persistent proteinuria in males with each co-morbid condition was significantly higher than the incidence without it (Fig. 3a). In females, the annual incidence of proteinuria was highest in subjects with diabetes followed by reduced renal function and hypertension and each of them was also significantly higher than the incidence without each condition (Fig. 3b).

We then analyzed the risk factors for the incidence of proteinuria and persistent proteinuria. Significant risk factors for the incidence of proteinuria were age, hypertension, diabetes, reduced renal function, obesity, low HDL-C, hypertriglyceridemia, and heavy smoker (current smoker >1 pack/day) in male subjects. In females, we found the same trend in risk factors for the incidence of persistent proteinuria as in males except for low HDL, hypertriglyceridemia and alcohol consumption (Table 2). Low HDL was not a significant risk for the incidence of persistent proteinuria in females, whereas hypertriglyceridemia (≥300 mg/dl) was a higher risk factor in females than in males. For smoking habit, a significant risk for incidence of persistent proteinuria was observed in both previous and current smoker in males.

Discussion

Diabetic nephropathy, CGN, and hypertensive nephropathy are three universal major primary renal diseases leading to ESRD. For the purpose of early detection of diabetic nephropathy or hypertensive nephropathy, selective screening of patients with diabetes or hypertension might be preferable. However, we should take into account that the prevalence and incidence of ESRD due to CGN are

Table 1 Baseline characteristics of the subjects divided by sex

	Males		Females	
Subjects in the study (*N*)	81,854		155,256	
Age[a]	60.2	9.7	56.8	10.2*
Follow-up duration (person-years)	330,614		687,381	
Non-hypertensive, non-diabetic[b]	36,567	44.7 %	89,360	57.6 %*
Non-hypertensive, diabetic[b]	2,410	2.9 %	2,171	1.4 %*
Hypertensive, non-diabetic[b]	39,115	47.8 %	60,301	38.8 %*
Hypertensive, diabetic[b]	3,762	4.6 %	3,424	2.2 %*
GFR <60 ml/min/ 1.73 m^2 [b]	4,272	5.20 %	9,643	6.2 %*
Total cholesterol (mg/dl[a])	196.5	34.1	209.9	35.2*
HDL-C (mg/dl[a])	52.8	14.6	58.4	14.5*
TG (mg/dl[a])	151.6	100.4	131	78.4*
Body mass index[a]	23.4	2.9	23.4	3.2
Smoking				
Current[b]	38,847	47.5 %	9036	5.9 %*
Previous[b]	24,103	29.4 %	1,219	0.8 %*
Alcohol consumption				
Occasional[b]	12,019	14.7 %	13,857	8.9 %*
Ethanol <20 g/day[b]	39,135	47.8 %	6,854	4.4 %*
Ethanol >20 g/day[b]	4,468	5.5 %	192	0.1 %*

* $p < 0.05$

[a] Mean, SD

[b] *N* (%)

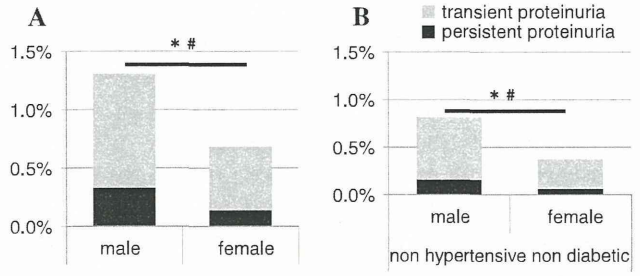

Fig. 2 The annual incidence of proteinuria and persistent proteinuria. *Black and gray bar* indicates the annual incidence of persistent proteinuria and transient proteinuria, respectively. A total of *stacked bars* mean annual incidence of proteinuria. The incidence of proteinuria and persistent proteinuria in males and females with any comorbid conditions (**a**) or without hypertension and diabetes (**b**) was demonstrated. Statistical significant value between males and females was indicated as: *asterisks* the incidence of proteinuria and *ash symbols* persistent proteinuria

different among races and geographic areas [4, 21–25]. Moreover, early detection of asymptomatic CGN without hypertension or diabetes strongly depends on urinalysis performed when screening the general population.

For a definitive diagnosis of CKD, at least 2 consecutive positive results of proteinuria with an interval of >3 months are required. To date, there has been no report on the annual incidence of persistent proteinuria in the general population.

In the present study, the incidence of persistent proteinuria in the general population was one-quarter of the incidence of proteinuria with an estimated 3,298 cases per million per year (1 patient per 303 person-years) in males and 1,379 cases per million per year (1 patient per 725 person-years) in females.

Previously, Brantsma et al. reported that the annual incidence of microalbuminuria was 1.02 % in both genders [26]. By using urine dipsticks we found an annual incidence of proteinuria of 1.20 % in males and 0.64 % in females. Furthermore, the incidences of proteinuria in our study were 37–81 times higher than in previous reported incidences in the non-hypertensive and non-diabetic population [0.01 % (0.001–0.1 %)] [5, 27]. In Japan, because of the high annual incidence of proteinuria among the non-hypertensive and non-diabetic population including CGN, frequent universal urinalysis screening might be preferable. As well as the incidence of proteinuria, the incidence of persistent proteinuria was higher in subjects with hypertension, diabetes or reduced renal function than in subjects without these conditions in both genders. Among incident proteinuria, 74.7 % of males and 79.8 % of females had transient proteinuria. Using 24-h urinary albumin excretion, albuminuria was diminished in 27.8 % of the subjects for a median follow-up duration of 4.2 years [26]. Using dipstick urinalysis, we have higher false positive results due to urine concentration or other non-pathological conditions. However, it is important to know aging, hypertension, diabetes, reduced renal function, obesity, dyslipidemia and smoking habit were strong risk factors for developing persistent proteinuria in both males and females. Further studies are needed to confirm the effect of controlling those factors on the incidence of both proteinuria and persistent proteinuria in a large population.

Our study has the advantage of a large sample size and availability of serial data. Moreover, this is the first report to show the incidence of persistent proteinuria in a community-based frequent follow-up study. However, it also has several limitations. Firstly, the participants of this study were from a community-based general population, but there was a lack of subjects aged <40 years old. Secondly, there was no data about detailed underlying renal diseases in our subjects.

In conclusion, our study aimed to determine the incidence of persistent proteinuria and its risk factors, and this is the first report to show the incidence of persistent proteinuria in the general population. As a result, the annual incidence of persistent proteinuria was 0.33 % in males and 0.14 % in females. The incidence of persistent proteinuria among the hypertensive, diabetic or reduced renal function

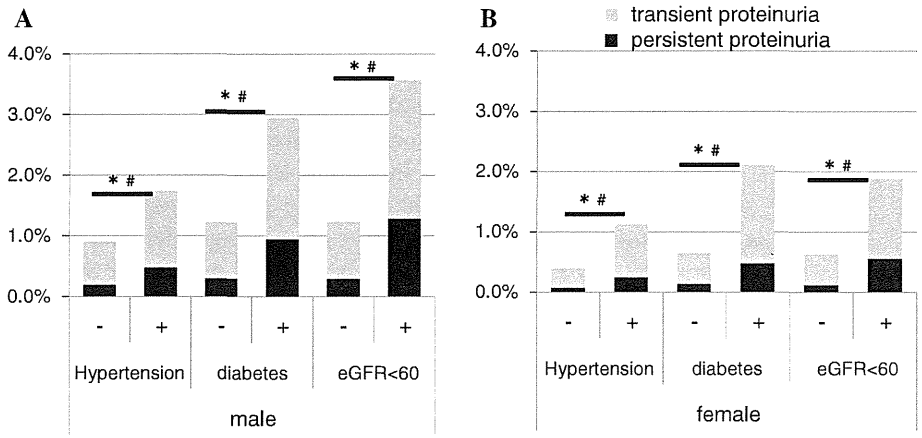

Fig. 3 The different annual incidence between the presence and absence of co-morbid conditions. *Black and gray bar* indicates the annual incidence of persistent proteinuria and transient proteinuria. A total of *stacked bars* mean annual incidence of proteinuria. Every co-morbid condition was significantly higher than without it (**a**, **b**). In any condition >20 % in males (**a**) and >16 % in females (**b**) with proteinuria in the 2nd year had persistent positive results for proteinuria. Statistical significant value between presence and absence of co-morbid conditions was indicated as: *asterisks* the incidence of proteinuria and *ash symbols* persistent proteinuria

Table 2 Multivariate analysis of predictors for developing persistent proteinuria

Predictors at first year	Male			Female		
	HR	95 % CI	*p*	HR	95 % CI	*p*
Age	1.03	1.022–1.04	<0.0001*	1.024	1.016–1.032	<0.0001*
Non-hypertensive, non-diabetic	1.00					
Non-hypertensive, diabetic	3.532	2.627–4.75	<0.0001*	3.534	2.338–5.341	<0.0001*
Hypertensive, non-diabetic	2.052	1.761–2.39	<0.0001*	2.477	2.116–2.898	<0.0001*
Hypertensive, diabetic	5.216	4.239–6.42	<0.0001*	5.62	4.315–7.319	<0.0001*
GFR <60 ml/min/1.73 m^2	3.097	2.637–3.64	<0.0001*	2.827	2.392–3.340	<0.0001*
Body mass index >25	1.511	1.332–1.71	<0.0001*	1.649	1.446–1.880	<0.0001*
Total cholesterol ≥220 mg/dl	1.075	0.934–1.24	0.3105	1.103	0.968–1.258	0.1401
HDL-C <35 mg/dl	1.387	1.144–1.68	0.0009*	1.008	0.729–1.393	0.9609
TG 150–299 mg/dl	1.25	1.096–1.43	0.0009*	1.449	1.261–1.666	<0.0001*
TG >300 mg/dl	1.249	0.992–1.57	0.0583	1.815	1.41–2.336	<0.0001*
Previous smoking	1.26	1.07–1.49	0.0058	1.537	0.765–3.091	0.2273
Current smoking <1 pack/day	1.48	1.09–2.02	0.0134*	1.419	0.934–2.157	0.1014
Current smoking >1 pack/day	1.44	1.23–1.7	<0.001*	1.44	0.97–2.137	0.0707
Occasional drinker	0.99	0.82–1.19	0.891	0.816	0.603–1.104	0.1879
Ethanol <20 g/day	0.85	0.74–0.97	0.0195*	1.012	0.71–1.442	0.9486
Ethanol >20 g/day	0.91	0.68–1.21	0.5067			

95 % CI 95 % confidence interval

* $p < 0.05$

population was much higher than among the normal population. By annual urinalysis screening of the general population, we detected that 1 out of 303 male subjects and 1 out of 725 female subjects developed CKD due to persistent proteinuria every year in Japan.

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Conflict of interest None declared.

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ORIGINAL ARTICLE

Effect of glomerular filtration rate and proteinuria on medical cost among screened subjects

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Abstract
Background Chronic kidney disease is a predictor of end-stage renal disease (ESRD) and cardiovascular disease (CVD). Therefore, the medical expenses are higher with the decrease in glomerular filtration rate (GFR). However, few studies have examined the medical expenses according to the baseline GFR.
Methods We investigated the relationship between GFR at health checks and medical expenses, combining the registries of both the health checks and report of medical expenses (receipts). The health checks were done from April 2008 to March 2009, and the eligible subjects were covered by the Okinawa Branch of the Japan Health Insurance Association. All reports of medical expenses were reviewed from April 2008 to March 2010 (24 months).
Results A total of 74,354 subjects, 38.2 % females with the mean age of 48.1 years, were examined according to whether they had visited medical facilities during the study period. The total number of receipts was 773,276. The average receipt point, 1 point = 10 Yen, was 686,410 (eGFR < 15), 56,408 (eGFR 15–29), 47,263 (eGFR 30–44), 24,372 (45–59), 16,018 (eGFR 60–74), 13,893 (eGFR 75–89), 13,990 (eGFR 90–104), 14,717 (eGFR 105–119), and 19,139 (eGFR 120 and over), respectively. The relationship between eGFR and medical expense was U-shaped, and the expense was lowest at eGFR 75–89.
Conclusion We demonstrate that the medical expenses increase as eGFR decreases. Subjects with higher eGFR, 120 and over, seemed to have higher medical expenses.

Keywords eGFR · Proteinuria · Medical cost · Outcomes

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Introduction

Chronic kidney disease (CKD) is a non-conventional risk factor for cardiovascular disease and mortality [1–3]. Moreover, patients with CKD often progress to end-stage renal disease (ESRD), which usually requires expensive treatment modalities. Early detection of CKD and early initiation of treatment are recommended to prevent these complications, but a cost-benefit analysis of universal screening has not been performed in the general population. Targeted screening for high-risk groups, such as those with diabetes mellitus (DM) and hypertension, is recommended, and the cost-effectiveness of universal screening for proteinuria has been questioned [4]. Some argue for population-based strategies, such as mass screening, in Asian countries [5]. In Japan, there is a long history of mass screening, including dipstick urine testing of school children and adults since the 1970s [6]. For workers 40 years of age and over, both urinalysis and measurement of serum creatinine have been mandated since 1992.

Primary causes of ESRD and the incidence of cardiovascular disease differ among ethnic groups [7]. Glomerulonephritis is the second leading cause of ESRD in Japan [8]. Proteinuria is an important predictor of both cardiovascular disease and ESRD. In the recent Kidney Disease: Improving Global Outcomes classification, the degree of

proteinuria was added to the estimated glomerular filtration rate (eGFR) criteria [9]. To our knowledge, however, the precise relationship between eGFR and proteinuria including medical expense has not been analyzed.

We analyzed the data of screenees of the Okinawa branch of the Japan Health Insurance Association and the subsequent medical costs in order to provide concrete evidence for policy makers on mass screening [10]. We hypothesized that baseline eGFR and proteinuria have a significant impact on future medical costs.

Methods

Screening

Subjects for this study were the participants in the 2008 screening performed by the Japan Health Insurance Association (Kyokai-Kenpo) from April 2008 to March 2009 in Okinawa. This screening was aimed to promote health among workers, and therefore spouses and children were not included. The numbers of target employees and offices were 241,828 persons and 15,530 sites in Okinawa. Employees were asked to visit nearby contracted clinics or hospitals ($N = 26$). There were 137,300 people in the target age group of 35–74 years, and a total of 74,313 (54.1 %) participated in the 2008 screening. We excluded those without pertinent clinical data ($N = 8$) and therefore analyzed a total of 74,305 subjects for this study.

The clinical and laboratory data are summarized in Table 1. Serum creatinine was measured using the enzymatic method, and eGFR (ml/min/1.73 m^2) was calculated using the formula of the Japanese Society of Nephrology [11]. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m^2), and obesity was defined as BMI $\geq$ 25 kg/m^2. DM was defined as fasting plasma glucose of at least 126 mg/dl, hemoglobin A1c of at least 6.1 % or being on medication to treat DM. Hypertension was defined as either blood pressure of at least 140/90 mmHg or being on anti-hypertension medication. Dyslipidemia was defined as triglyceride levels of at least 150 mg/dl, HDL cholesterol under 40 mg/dl or being on medication.

Table 1 Background of the screened subjects (total 74,305)

Age (years)	48.1 (8.6), 35–74
Females [*n* (%)]	28,398 (38.2 %)
Body mass index (kg/m^2)	24.1 (3.8)
Systolic blood pressure (mmHg)	122.5 (18.1)
Diastolic blood pressure (mmHg)	76.6 (12.1)
Total cholesterol (mg/dl)	203.8 (34.5)
Triglyceride (mg/dl)	131.8 (113.4)
HDL cholesterol (mg/dl)	59.4 (15.5)
Fasting plasma glucose (mg/dl)	100.1 (22.4)
Hemoglobin A1c (%)	5.3 (0.8)
Uric acid (mg/dl)	5.6 (1.5)
Proteinuria (%)	
Negative ($N = 61,211$)	82.4 %
Trace ($N = 8,476$)	11.4 %
1+ ($N = 2,590$)	3.5 %
2+ and over ($N = 1,094$)	1.5 %
Not tested ($N = 892$)	1.2 %
Serum creatinine (mg/dl)	0.8 (0.3)
eGFR (ml/min/1.73 m^2)	81.0 (15.4)
<15 ($N = 68$)	0.1 %
15–29 ($N = 71$)	0.1 %
30–44 ($N = 251$)	0.3 %
45–59 ($N = 3,861$)	5.2 %
60–74 ($N = 22,236$)	29.9 %
75–89 ($N = 30,093$)	40.5 %
90–104 ($N = 13,140$)	17.7 %
105–119 ($N = 3,448$)	4.6 %
120 ($N = 1,137$)	1.5 %
Smoker (%)	33.0 % (men 44.4 %, women 14.6 %)
Comorbid conditions	
Diabetes mellitus	7.0 %
Hypertension	28.7 %
Dyslipidemia	31.6 %

Screening was performed from April 2008 to March 2009. Data are represented as mean (SD). Most of the laboratory data were available for more than 98 % of the total. Hemoglobin A1c was tested in only 5,998 screenees (8.1 %) as it was indicated only in those with suspected diabetes mellitus. The definition of diabetes mellitus was fasting plasma glucose $\geq$126 mg/dl, hemoglobin A1c $\geq$6.1 % or being on medication. Hypertension was considered as either blood pressure of $\geq$140/90 mmHg or being on medication. Dyslipidemia was indicated by triglyceride level $\geq$150 mg/dl, HDL cholesterol level <40 mg/dl or being on medication

Medical costs (receipts)

All monthly medical expense receipts were sent to the Japan Health Insurance Association from each medical facility. All medical procedures, such as examinations, laboratory tests, surgery and others, were coded by a point score (1 point = 10 Yen) and summarized (receipt score). After a survey by an independent agency, the Japan Health Insurance Association reimburses the medical expenses to each facility. Enrolled screenees are coded with a unique identification number. During the study period of April 2008 to March 2010, there were 773,276 receipts submitted for the screenees. All receipts after the screening were summarized for each subject until disenrollment or by March 2010.

Statistical analysis

Analyses were performed using an anonymously coded analysis data set provided by the Okinawa Branch of the Japan Health Insurance Association. Continuous data were expressed as mean (standard error, SE) and skewed data as median. Baseline characteristics are presented for the total study population and stratified by quartile range of the receipt score. All P-values less than 0.05 were considered statistically significant. All analyses were conducted using SAS software (version 8.2).

Results

We studied 74,305 subjects with a total of 1,338,210 subject-months: median follow-up was 18 months (interquartile range, 15–21 months). Mean subject age was 48.1 years, ranging from 35 to 74 years. The prevalence of CKD (eGFR < 60) and proteinuria (≥1+ by dipstick) was 5.7 and 5.0 %, respectively. Subjects with eGFR less than 15 ($N = 68$) were excluded from the following analyses as the receipt scores of this group were exceedingly high (mean 29,700 per month) compared with those with an eGFR of 15 or more. The baseline characteristics are summarized in Table 1.

Mean (median) receipt point score was 766 (259) subject-months, ranging from 0 to 1,633,050. Overall, 14.6 % of subjects dis-enrolled for various reasons during the follow-up.

The clinical demographics by quartile of receipt score are summarized in Table 2. Higher scores were related to subjects who were older; had a larger BMI; had a lower eGFR; and had a higher prevalence of proteinuria, DM, hypertension, and dyslipidemia. Unexpectedly, smokers had lower receipt scores. The mean (SE) receipt score per subject-month was 1,756 (65) for DM ($n = 5,165$), 1,328 (88) for non-DM with proteinuria ($n = 2,871$), and 698 (9) for non-DM without proteinuria ($n = 66,269$).

Receipt score per subject-month was significantly associated with the baseline levels of eGFR (Fig. 1a), proteinuria (Fig. 1b), and their combination (Fig. 1c). Receipt score increased with decreasing eGFR and increasing degrees of proteinuria. The receipt score was lowest in subjects with eGFR between 90 and 104 without proteinuria. The receipt score increased in subjects with high eGFR (≥120). The significance of the effect of selected variables on a high receipt score of 2,524 points per month, which comprised 95 % or more of the studied population, is summarized in Table 3.

The relation between age and mean (SE) receipt score per subject-month by the presence or absence of a low eGFR (eGFR < 60) is shown in Fig. 2a. In any age group other than those 35–39 years, subjects with proteinuria had a higher receipt score (Fig. 2b). The mean (SE) receipt score per subject-month was 699 (9) in non CKD ($n = 68,136$), 1,289 (79) in CKD without proteinuria

Table 2 Clinical demographics by quartile of receipt score, per subject-month

Receipt score Points per month	Q1 0–73	Q2 74–259	Q3 260–680	Q4 681–
Number	18,729	18,474	18,495	18,539
Age (years)	45.7 (7.7)	46.0 (7.8)	48.7 (8.3)	52.0 (9.1)
Males (%)	69.7	61.2	56.0	60.0
BMI (kg/m^2)	23.8 (3.6)	23.8 (3.6)	24.1 (3.8)	24.8 (4.0)
eGFR (ml/min/1.73 m^2)	82.5 (14.3)	82.0 (14.6)	80.8 (15.1)	79.1 (16.6)
Proteinuria (%)	4.0	3.5	4.9	7.4
Uric acid (mg/dl)	5.7 (1.5)	5.6 (1.5)	5.6 (1.5)	5.7 (1.5)
Smoker (%)	41.2	34.6	28.9	27.2
DM (%)	3.4	3.0	6.2	15.2
Hypertension (%)	18.6	18.3	31.4	46.5
Dyslipidemia (%)	29.3	28.3	30.9	37.9
Receipt score	20 (25)	158 (53)	439 (120)	2,451 (4,474)
Follow-up, months	15.7 (6.7)	17.5 (4.4)	16.9 (5.0)	16.1 (5.7)
Disenrollment (%)	15.5	8.2	13.9	20.8

Data are represented as mean (SD). Proteinuria denotes ≥1+ by dipstick. Hyperuricemia denotes serum uric acid ≥7.0 mg/dl in both sexes. DM was defined as having fasting plasma glucose ≥126 mg/dl, hemoglobin A1c ≥6.1 %, or being on medication. Hypertension was defined as either having blood pressure ≥140/90 mmHg or being on medication. Dyslipidemia was defined as having triglyceride levels ≥150 mg/dl, HDL cholesterol levels <40 mg/dl, or being on medication

BMI body mass index, *DM* diabetes mellitus

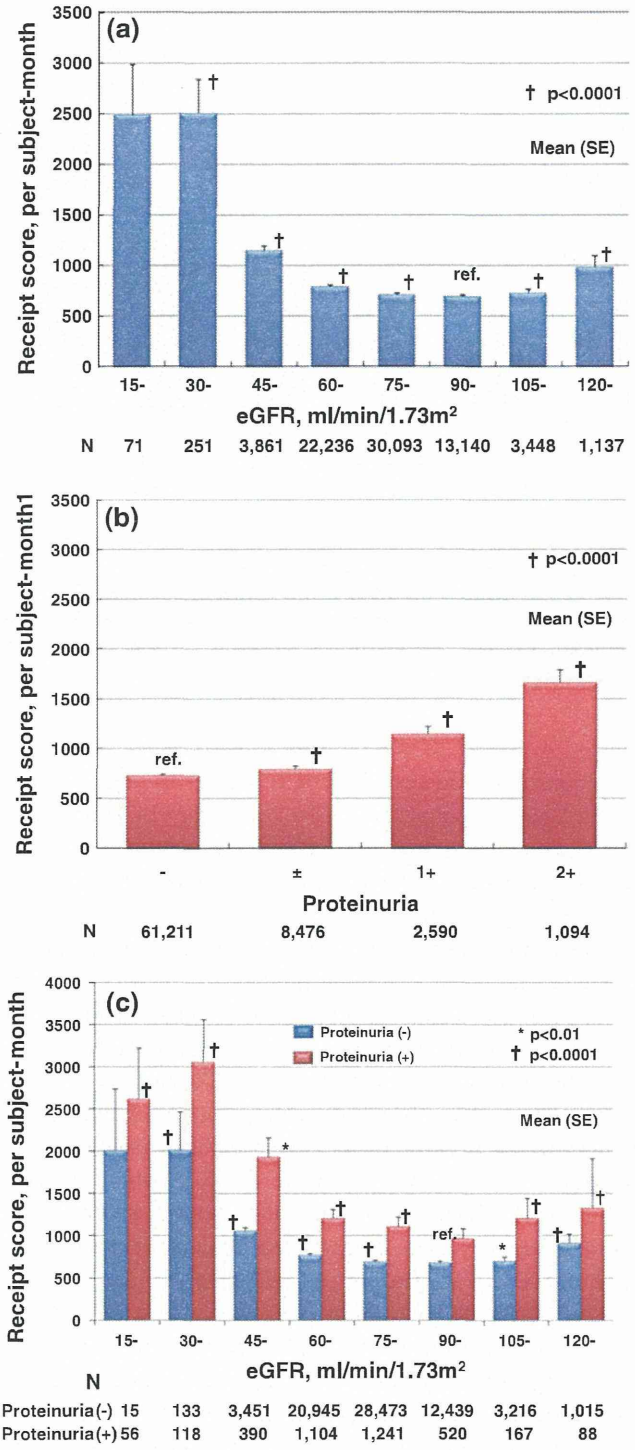

Fig. 1 **a** Relation between baseline eGFR (ml/min/1.73 m^2) and mean (SE) receipt score, per subject-month. **b** Relation between baseline proteinuria and mean (SE) receipt score, per subject-month. Subjects with eGFR < 15 ml/min/1.73 m^2 ($N = 68$) were excluded. **c** Relation between the combination of baseline eGFR (ml/min/1.73 m^2) and proteinuria (dipstick ≥1+) and mean receipt score, per subject-month. *P*-values are <0.01 (*), <0.001 (**), and <0.0001 (†) (age and sex adjusted)

Table 3 Significance of effect selected variables on a high receipt score of at least 95 % (>2,524 points per month)

Variables	Adjusted odds ratio (95 % CI)	*P* value
eGFR (ml/min/1.73/m^2)		
15–29	9.23 (5.51–15.48)	<0.0001
30–44	5.74 (4.18–7.88)	<0.0001
45–59	2.22 (1.93–2.55)	<0.0001
60–74	1.17 (1.06–1.30)	0.0029
75–89	1.03 (0.94–1.14)	NS
90–104	Reference	
105–119	1.13 (0.94–1.34)	NS
120–	1.38 (1.06–1.79)	0.0164
Proteinuria		
Negative	Reference	
Trace	1.07 (0.96–1.18)	NS
1+	1.67 (1.44–1.94)	<0.0001
2+ and over	3.17 (2.66–3.78)	<0.0001
Body mass index (kg/m^2)		
<18.0	Reference	
18.0–24.9	0.91 (0.73–1.14)	NS
25.0–29.9	1.18 (0.94–1.48)	NS
30.0–	1.61 (1.26–2.05)	0.0001
	χ^2 score	*P* value
Elderly (vs. 35–64 years)	836.8	<0.0001
Males (vs. females)	8.2	0.0042
Smoker (vs. non-smoker)	14.9	0.0001
Diabetes mellitus (vs. No-DM)	694.1	<0.0001
Hypertension (vs. no-hypertension)	513.9	<0.0001
Dyslipidemia (vs. no-dyslipidemia)	86.8	<0.0001

Elderly denotes being 65–74 years old. Body mass index was categorized into four groups in both men and women as <18, 18–24.9, 25–29.9, and 30 and over. Adjusted odds ratio (95 % CI): adjusted for age and sex. For eGFR categories, data were adjusted for age, sex, and variables in this table. Receipts are sent to the association from each medical facility describing all medical expenses for each month. One point is equal to 10 yen

NS not significant

($n = 3{,}106$), and 3,857 (389) in CKD with proteinuria ($n = 529$).

The receipt score was higher in every age-class when associated with low eGFR. The difference in receipt score by eGFR became smaller in higher age classes, but particularly in those aged 65–74 years. The effect of number of co-morbid conditions is summarized in Fig. 3. The higher the number of comorbid conditions is, the higher the medical costs.