

**Table 1** Demographics of the screened cohorts. Screening was performed during April 1, 2008 to March 31, 2009

Number of participants	332,174		
Men (%)	134,751 (40.6)		
Age (years)	63.6 (8.3), 40–74		
Body height (cm)	157.2 (8.5)	Men 164.6 (6.3) <sup>#</sup>	Women 152.2 (5.7)
Body weight (kg)	57.6 (10.5)	Men 64.5 (9.5) <sup>#</sup>	Women 52.8 (8.3)
Body mass index (kg/m <sup>2</sup> )	23.2 (3.3)	Men 23.8 (3.1) <sup>#</sup>	Women 22.8 (3.5)
Waist circumference (cm)	84.1 (9.2)	Men 85.7 (8.3) <sup>#</sup>	Women 83 (9.5)
Systolic blood pressure (mmHg)	128.9 (17.4)		
Diastolic blood pressure (mmHg)	76.3 (10.7)		
Fasting blood glucose (mg/dl)	98.2 (21.5)		
Hemoglobin A1c (%)	5.3 (0.7)		
Triglyceride (mg/dl)	122.5 (84.0)		
HDL cholesterol (mg/dl)	62.1 (16.3)		
LDL cholesterol (mg/dl)	125.9 (30.6)		
Hemoglobin (g/dl)	13.6 (1.4)		
Serum creatinine (mg/dl)	0.7 (0.2)	Men 0.8 (0.3) <sup>#</sup>	Women 0.6 (0.2)
eGFR (ml/min/ 1.73 m <sup>2</sup> )	75.0 (16.2)		
<15	240 (0.07%)		
15–29	655 (0.20%)		
30–44	4,300 (1.29%)		
45–59	42,975 (12.94%)		
60–89	225,081 (67.76%)		
≥90	58,923 (17.74%)		
Serum uric acid (mg/dl)	5.2 (1.4)	Men 6.0 (1.3) <sup>#</sup>	Women 4.7 (1.1)
Glucosuria <sup>a</sup>	2.30%		
Proteinuria <sup>a</sup>	5.40%		
Hematuria <sup>a</sup>	7.50%		
Past history (%)			
Stroke	3.30		
Cardiac disease	6.00		
Kidney disease	0.70		
Medication (%)			
Anti-hypertensive drugs	28.80		
Lipid lowering drugs	15.80		

**Table 1** continued

Insulin or hypoglycemic drugs	5.20		
Lifestyle (%)			
Smoking	13.50	Men 25.2% <sup>#</sup>	Women 5.5%
Drinking	44.30	Men 65.2% <sup>#</sup>	Women 30.0%

Data are mean (SD)

<sup>a</sup> Positive urine test denote ≥1+ by dipstick<sup>#</sup> *P* < 0.01 (vs women)

proteinuria and having an eGFR ≥90 ml/min/1.73 m<sup>2</sup>. The combination of higher levels of proteinuria and lower levels of eGFR was associated with an increased prevalence of a history of CVD (Fig. 2).

Mean (SD) levels of BMI and smoking rate are summarized in Table 4. Both BMI and smoking rate were higher in men than in women. The smoking rate tended to decrease in the lower eGFR category.

## Discussion

The target population of this screening in Japan comprised participants from 40 to 74 years of age, and the expected turnout was approximately 58 million. In the 2008 screening, the actual participation rate remained low, 20–30%, probably because of the lack of preparation for implementing this new system. The total number of participants in the present study was approximately 0.58 million; therefore, our analysis included at least 1% of the target population in Japan.

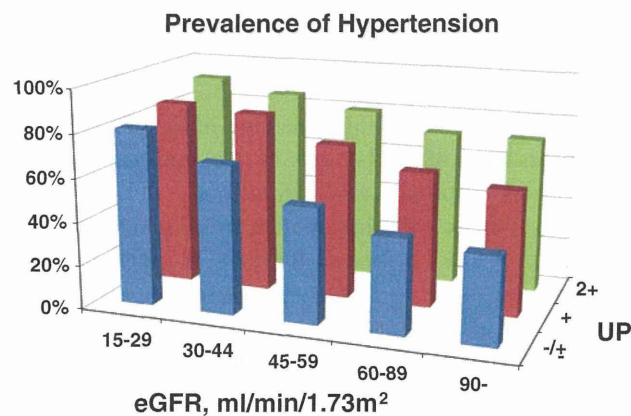
The results revealed the current health status among the general Japanese population. The proportion of the population comprising elderly people is high in Japan and its rate of increase is currently the highest in the world. The proportion of those with a low GFR (<60 ml/min/1.73 m<sup>2</sup>), regardless of proteinuria, increases with aging. Fortunately, the rate of decline of the GFR in the Japanese is relatively low, 0.36 ml/min/1.73 m<sup>2</sup>/year [9]. Elderly people are at risk for CVD and death. Effective strategies to establish a health check and guidance system are necessary to better accommodate the future burden of medical and social costs due to the aging population. Based on the findings of the present study, we propose that a cost–benefit analysis be performed on programs designed for the early detection and treatment of CKD, including education regarding lifestyle modification.

CVD is a recently recognized risk factor for CKD and ESRD [7]. The prevalence of CVD in CKD stage 5 is

**Table 2** Prevalence of obesity, DM, and hypertension based on the combination of eGFR and proteinuria

	eGFR	Proteinuria	Number (%)	Obesity (%)	DM (%)	Hypertension (%)
	<15	Minus, ±	101 (0.03)	22.8	10.2	50.5 <sup>#</sup>
		1+	35 (0.01)	28.6	17.6	88.6*
		≥2+	103 (0.03)	31.1	32.0*	92.2*
	15–29	Minus, ±	251 (0.08)	29.1	25.2*	81.1*
		1+	119 (0.04)	31.1	22.7*	85.5*
		≥2+	285 (0.09)	40.3*	38.4*	91.9*
	30–44	Minus, ±	3,194 (0.96)	35.8*	13.9*	68.2*
		1+	504 (0.15)	43.8*	24.9*	83.3*
		≥2+	579 (0.17)	46.5*	33.9*	85.9*
	45–59	Minus, ±	39,265 (11.82)	30.7*	9.3*	52.7*
		1+	2,408 (0.72)	42.2*	19.6*	71.6*
		≥2+	1,326 (0.40)	49.5*	31.1*	80.2*
	60–89	Minus, ±	214,768 (64.66)	25.4*	8.4*	43.3*
		1+	7,579 (2.28)	38.5*	19.3*	62.1*
		≥2+	2,703 (0.81)	46.5*	31.1*	72.0*
	≥90	Minus, ±	56,495 (17.01)	24.3	10.6	39.8
		1+	1,812 (0.55)	37.9*	26.5*	57.4*
		≥2+	647 (0.19)	46.5*	36.4*	72.0*

Total number of participants was 332,174. Parentheses are the percentage to the total participants in each column. Obesity, BMI ≥25 kg/m<sup>2</sup>; DM, HbA1c ≥6.1% or on treatment; hypertension, 140/90 mmHg or on treatment  
\* *P* < 0.0001, <sup>#</sup>*P* < 0.05 (vs. reference value of eGFR ≥90 and proteinuria minus or ±)



**Fig. 1** Prevalence of hypertension by the combination of eGFR and proteinuria. Prevalence of hypertension was significantly (*P* < 0.0001) higher in every column except those with eGFR 15–29 and proteinuria minus or (±) (*P* < 0.05) when compared to the reference value of eGFR ≥90 and proteinuria minus or (±)

approximately 25%; similar to the prevalent dialysis population. Ethnic variations in CVD incidence and subtype are well described in the general population [10, 11]. The stroke mortality rate is high in Japan; however, in the present study, the prevalence of stroke was lower than that of cardiac disease (Table 1). The reasons for this finding are not clear, but many people with stroke are unable to participate in this type of screening program.

Metabolic syndrome is an important risk factor for developing CKD [12], and for DM and hypertension, which are the main causes of ESRD [13]. We previously reported

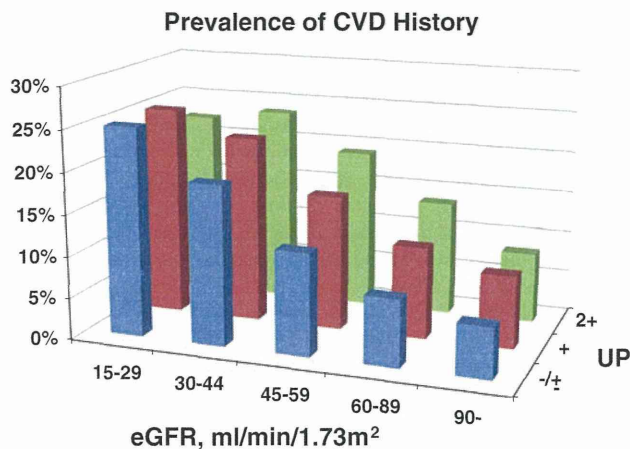
**Table 3** Prevalence of history of stroke and heart disease based on the combination of eGFR and proteinuria

eGFR	Proteinuria	Stroke	Heart Disease	CVD
<15	Minus, ±	4.0	6.9	10.9*
	1+	5.7	17.1*	22.9
	≥2+	8.7*	12.6	19.4 <sup>#</sup>
15–29	Minus, ±	13.9*	15.9*	25.1*
	1+	15.1*	15.1*	25.2*
	≥2+	11.6*	13.7*	22.5*
30–44	Minus, ±	8.6*	13.1*	19.2*
	1+	9.9*	16.1*	22.4*
	≥2+	10.5*	16.4*	23.7*
45–59	Minus, ±	4.8*	8.5*	12.3*
	1+	6.9*	11.7*	16.2*
	≥2+	8.3*	13.1*	19.2*
60–89	Minus, ±	3.0*	5.6*	8.1*
	1+	4.7*	7.3*	11.1*
	≥2+	5.8*	9.3*	13.8*
≥90	Minus, ±	2.4	4.1	6.1
	1+	3.5 <sup>†</sup>	6.0*	8.8*
	≥2+	4.5 <sup>†</sup>	4.6	8.5 <sup>†</sup>

Total number of participants was 332,174. Cardiovascular disease (CVD) denotes stroke and/or heart disease

\* *P* < 0.0001, <sup>†</sup>*P* < 0.02, <sup>#</sup>*P* < 0.05 (vs reference value of eGFR ≥90 and proteinuria minus or ±)

the significance of obesity in the risk for ESRD. Recent societal changes in lifestyle related to motorized transportation and high-calorie intake may have contributed to the



**Fig. 2** Prevalence of history of cardiovascular disease (CVD) by the combination of eGFR and proteinuria. Prevalence of CVD was significantly ( $P < 0.0001$ ) higher in every column except those with eGFR 15–29; not significant for proteinuria (+), and  $P < 0.05$  for proteinuria  $\geq 2+$ , when compared to the reference value of eGFR  $\geq 90$  and proteinuria minus or ( $\pm$ ).  $P$  value was  $<0.02$  for those with eGFR  $\geq 90$  and proteinuria  $\geq 2+$

**Table 4** Mean (SD) levels of body mass index (BMI) and smoking rate in each sex based on the combination of eGFR and proteinuria

eGFR	Proteinuria	Men		Women	
		BMI (kg/m <sup>2</sup> )	Smoker (%)	BMI (kg/m <sup>2</sup> )	Smoker (%)
<15	Minus, $\pm$	24.1 (2.6)	5.4	22.2 (3.0)	10.9
	1+	24.2 (2.4)	12.5	22.0 (3.4)	5.3
	$\geq 2+$	23.3 (2.8)	22.2	24.5 (4.7)	2.5
15–29	Minus, $\pm$	23.6 (3.1)	15.0	23.6 (4.1)	8.0
	1+	24.5 (3.4)	7.0	23.5 (3.8)	6.5
	$\geq 2+$	24.2 (3.1)	18.4	25.3 (4.7)	6.0
30–44	Minus, $\pm$	24.3 (2.9)	15.3	23.7 (3.8)	4.4
	1+	24.8 (3.5)	19.5	24.2 (4.5)	6.6
	$\geq 2+$	25.2 (3.2)	19.5	24.9 (4.4)	5.9
45–59	Minus, $\pm$	24.1 (2.8)	15.8	23.2 (3.4)	3.9
	1+	24.7 (3.0)	20.6	24.2 (4.2)	5.7
	$\geq 2+$	25.2 (3.5)	24.9	25.1 (4.4)	5.7
60–89	Minus, $\pm$	23.7 (3.0)	24.4	22.7 (3.4)	5.1
	1+	24.5 (3.4)	29.4	23.9 (4.3)	6.8
	$\geq 2+$	25.1 (3.8)	31.2	24.8 (4.8)	8.1
$\geq 90$	Minus, $\pm$	23.4 (3.4)	38.8	22.7 (3.6)	7.2
	1+	24.2 (4.0)	46.5	24.2 (4.5)	8.3
	$\geq 2+$	25.0 (4.2)	39.5	25.0 (5.0)	9.4

Total number of participants was 332,174  
SD standard deviation

increased prevalence of obesity. Although the prevalence of obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) is lower in Japan than in the USA [14], complications begin to increase in the Japanese after reaching a BMI of 25 kg/m<sup>2</sup>.

Microalbuminuria is suspected when the dipstick test results for proteinuria are ( $\pm$ ) and/or 1+ [15]. Routine measurement of microalbuminuria is not feasible for the universal screening of CKD, as the cost is much higher than that of a dipstick urine test for proteinuria. Japan has a long history of universal screening, including dipstick urine testing for both proteinuria and hematuria. A positive proteinuria test result has a strong predictive value for the development of ESRD.

The strengths of the present study are: the number of participants was sufficiently large. It is the first nationwide targeted screening program aimed at determining the prevalence of metabolic syndrome in Japan. People diagnosed with metabolic syndrome are entitled to receive instruction to modify their lifestyles and therefore the risk factors for CKD and CVD can be modified accordingly. The prevalence of metabolic syndrome and obesity, particularly in men, is increasing; therefore, the prevalence of CKD is increasing in Japan [16]. The combined eGFR and dipstick proteinuria test results indicate that the prevalence of risk factors for CKD and CVD increasing. Future follow-up studies will provide the predictive value of this CKD stratification on CVD, ESRD, and mortality.

The present study has several limitations. It is a cross-sectional study. Single tests for dipstick proteinuria and serum creatinine might cause misclassification of the true prevalence of CKD. To confirm the existence of CKD, the test should be repeated annually, at least 3 months apart. The current estimation of GFR used in this study is precise ( $<60$  ml/min/1.73 m<sup>2</sup>); therefore, the proportion of those with moderately decreased GFR ( $<45$  ml/min/1.73 m<sup>2</sup>) seems to be high, 1.56%. We selected patients with data for both serum creatinine and dipstick urine test, which comprised approximately two-thirds of the total participants. A cost–benefit analysis on the best combination of screening tests remains to be performed in Japan. Details of CVD, such as subtype of stroke and heart disease, are not clear. Risk factors may differ among diseases. Information of past medical history, medications, and lifestyle were obtained from a questionnaire, which has not yet been validated. Finally, the elderly population, those aged  $\geq 75$  years, was not considered in the present screening. It remains to be determined whether or not risk stratification based on both eGFR and proteinuria is applicable in this age group. CKD also has a role in medical problems commonly seen in elderly people, such as malignancies, pneumonia, sepsis, dementia, and bone fractures.

In conclusion, the risk profiles of CKD and CVD are indicated by the new CKD classification based on eGFR and proteinuria levels in the newly developed screening system used in Japan. Although CKD stratification based on the combined eGFR and proteinuria results seems to be a useful predictor of CVD and mortality in the general

population in Japan, the validity of this finding has yet to be demonstrated in outcome studies, and would be useful for the international comparison of the incidence of ESRD [17].

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**Conflict of Interest** None.

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## Cost-effectiveness of chronic kidney disease mass screening test in Japan

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### Abstract

**Background** Chronic kidney disease (CKD) is a significant public health problem. Strategy for its early detection is still controversial. This study aims to assess the cost-effectiveness of population strategy, i.e. mass screening, and Japan's health checkup reform.

**Methods** Cost-effectiveness analysis was carried out to compare test modalities in the context of reforming Japan's mandatory annual health checkup for adults. A decision tree and Markov model with societal perspective were constructed to compare dipstick test to check proteinuria only, serum creatinine (Cr) assay only, or both.

**Results** Incremental cost-effectiveness ratios (ICERs) of mass screening compared with do-nothing were calculated as ¥1,139,399/QALY (US \$12,660/QALY) for dipstick

test only, ¥8,122,492/QALY (US \$90,250/QALY) for serum Cr assay only and ¥8,235,431/QALY (US \$91,505/QALY) for both. ICERs associated with the reform were calculated as ¥9,325,663/QALY (US \$103,618/QALY) for mandating serum Cr assay in addition to the currently used mandatory dipstick test, and ¥9,001,414/QALY (US \$100,016/QALY) for mandating serum Cr assay and applying dipstick test at discretion.

**Conclusions** Taking a threshold to judge cost-effectiveness according to World Health Organization's recommendation, i.e. three times gross domestic product per capita of ¥11.5 million/QALY (US \$128 thousand/QALY), a policy that mandates serum Cr assay is cost-effective. The choice of continuing the current policy which mandates dipstick test only is also cost-effective. Our results suggest that a population strategy for CKD detection such as mass screening using dipstick test and/or serum Cr assay can be justified as an efficient use of health care resources in a

On behalf of The Japanese Society of Nephrology Task Force for the Validation of Urine Examination as a Universal Screening.

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population with high prevalence of the disease such as in Japan and Asian countries.

**Keywords** Chronic kidney disease · Cost-effectiveness · Dipstick test · Mass screening · Proteinuria · Serum creatinine

## Introduction

A consensus has been established that chronic kidney disease (CKD) is a worldwide public health problem [1, 2]. The effectiveness of its early detection and treatment to prevent progression to end-stage renal disease (ESRD) and premature death from cardiovascular disease has become widely accepted [3], while the strategy of its screening is still under debate [4]. Whereas high-risk strategies such as routine screening for diabetes patients and as a part of initial evaluation of hypertension patients are pursued in Western countries [5, 6], some argue that population strategies, such as mass screening, could be adopted in Asian countries where CKD prevalence is high [7].

Japan has a long history of mass screening programme for kidney diseases targeting school children and adults since the 1970s. Both urinalysis and measurement of serum creatinine (Cr) level have been mandated to detect glomerulonephritis in annual health checkup provided by workplace and community for adults aged  $\geq 40$  years old since 1992 [8]. However, glomerulonephritis was replaced as the leading cause of ESRD by diabetic nephropathy in 1998, and the focus of mass screening policy for adults was shifted to control of lifestyle-related diseases. In 2008, the Japanese government launched a programme, Specific Health Checkup (SHC) and Specific Counselling Guidance, focusing on metabolic syndrome in order to control lifestyle-related diseases, targeting all adults between the ages of 40 and 74 years [9]. This is a combined programme of mass screening followed by health education or referral to physicians. During the process of this development of SHC, different types of screening test for kidney diseases were discussed in the health policy arena [10]. Abandonment of dipstick test to check proteinuria was initially proposed by the Ministry of Health, Labour and Welfare, which was opposed by nephrologists who emphasised the significance of CKD. As a consequence, serum Cr assay was alternatively dropped and dipstick test remained in the list of mandatory test items [11]. However, those found with proteinuria in SHC are not included in the health education programme nor referred to physicians in the following Specific Counselling Guidance that particularly targets metabolic syndrome. At the time, much attention was paid to a report from the USA which suggested the cost-ineffectiveness of mass screening for proteinuria [12],

which encouraged the government to abandon dipstick test in their initial proposal.

From the viewpoint of CKD control, the current SHC and Specific Counselling Guidance are not adequate. Therefore, to present evidence regarding CKD screening test for the revision of SHC, which is due in 5 years from its start in 2008, the Japanese Society of Nephrology set up the Task Force for the Validation of Urine Examination as a Universal Screening. Since cost-effectiveness analysis provides crucial information for organising public health programmes such as mass screening, the task force conducted an economic evaluation as a part of their mission. This paper presents the value for money of CKD screening test demonstrated by the task force. The results have implications for CKD screening programmes not only in Japan but also for other populations with high prevalence of CKD such as in Asian countries.

## Methods

We conducted cost-effectiveness analysis of CKD screening test in SHC with a decision tree and Markov modelling from societal perspective in Japan. In modelling, we carried out a deliberate literature survey to find the best available evidence from Japan, while reports from overseas were excluded. The PubMed database and Iqaku Chuo Zasshi (Japana Centra Revuo Medicina), a Japanese medical literature database, were accessed with combinations of relevant terms such as CKD, health checkup etc. Additionally, we re-analysed our databases and carried out surveys where applicable.

### Participant cohort

We assume that uptake of SHC does not change regardless of the choice of the test used for CKD screening, so we model a cohort of participants in SHC. Since the sex and age distribution of participants affects outcomes, we run our economic model by sex and age strata. Probabilities of falling into a sex and age stratum are adopted from a nationwide complete count report of SHC in 2008 [13]. Each value is shown in Table 1, and we estimate outcomes based on the prognosis of participants by initial renal function. We also run our economic model for 25 initial renal function strata defined by the combination of five levels of dipstick test results and five stages of CKD according to estimated glomerular filtration rate (eGFR) derived from serum Cr level. Probabilities of falling into an initial renal function stratum are calculated from the Japan Tokutei-Kenshin CKD Cohort 2008, which is a large cohort for the evaluation of SHC. Each value is shown in Table 1.

**Table 1** Model assumptions

			Base-case value	Range tested in sensitivity analysis (%)	Source
<i>Participant cohort</i>					
Probability (%)					
Falling into sex and age stratum	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74	10.008, 9.280, 8.810, 9.783, 6.460, 5.721, 4.472	±50	[13]
	Female	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74	6.291, 6.054, 6.137, 7.364, 6.836, 7.143, 5.643		
Falling into initial renal function stratum	–	Stage 1, stage 2, stage 3, stage 4, stage 5	11.660, 46.095, 28.627, 0.224, 0.029	±50	Japan Tokutei-Kenshin CKD Cohort 2008
	±	Stage 1, stage 2, stage 3, stage 4, stage 5	0.866, 3.771, 3.214, 0.056, 0.008		
	1+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.325, 1.548, 1.779, 0.086, 0.013		
	2+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.080, 0.385, 0.705, 0.095, 0.026		
	≥3+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.027, 0.104, 0.204, 0.053, 0.020		
<i>Decision tree</i>					
Probability (%)					
Seeking detailed examination after screened as further examination required			40.0	±50	[15, 16] and expert opinion
Either eGFR <50 ml/min/1.73 m <sup>2</sup> or having comorbidity among stage 3 patients (advanced stage 3)			83.5	±50	Japan Tokutei-Kenshin CKD Cohort 2008
Starting CKD treatment after detailed examination	–	Advanced stage 3, stage 4, stage 5	48.9, 82.2, 96.0	±50	Delphi method survey of expert committee
	±	Advanced stage 3, stage 4, stage 5	51.7, 83.9, 97.1		
	1+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	25.6, 31.1, 46.7, 71.7, 92.2, 98.0		
	2+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	62.2, 68.3, 78.9, 93.2, 97.1, 99.8		
	≥3+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	93.2, 94.3, 97.1, 97.7, 99.9, 99.9		
<i>Markov model</i>					
Probability (%)					
From (1) screened and/or examined to (2) ESRD with no treatment by initial renal function	–	Stage 1, stage 2, stage 3, stage 4, stage 5	0.001, 0.004, 0.016, 0.154, 1.743	±50	Calculated from Okinawa database [18]
	±	Stage 1, stage 2, stage 3, stage 4, stage 5	0.019, 0.020, 0.036, 1.137, 5.628		
	1+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.036, 0.024, 0.303, 3.527, 15.802		
	2+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.080, 0.305, 1.170, 10.939, 31.409		
	≥3+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.347, 0.933, 2.506, 13.824, 69.340		

Table 1 continued

				Base-case value	Range tested in sensitivity analysis (%)	Source
From (2) ESRD to (5) death by sex and age	Male		40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90	0.033, 0.034, 0.035, 0.036, 0.038, 0.039, 0.041, 0.042, 0.044, 0.045, 0.047, 0.048, 0.050, 0.052, 0.054, 0.056, 0.058, 0.060, 0.062, 0.065, 0.068, 0.071, 0.074, 0.078, 0.081, 0.084, 0.088, 0.092, 0.097, 0.101, 0.105, 0.111, 0.117, 0.123, 0.129, 0.135, 0.142, 0.148, 0.155, 0.160, 0.166, 0.176, 0.186, 0.196, 0.202, 0.208, 0.226, 0.229, 0.245, 0.288, 0.257	±50	Calculated from Japanese dialysis patient registry [21]
	Female		40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90	0.029, 0.030, 0.031, 0.032, 0.033, 0.034, 0.035, 0.036, 0.038, 0.039, 0.041, 0.042, 0.043, 0.045, 0.047, 0.049, 0.050, 0.052, 0.055, 0.057, 0.059, 0.062, 0.065, 0.068, 0.070, 0.074, 0.078, 0.080, 0.085, 0.089, 0.093, 0.097, 0.101, 0.105, 0.110, 0.115, 0.122, 0.127, 0.134, 0.138, 0.145, 0.151, 0.159, 0.162, 0.173, 0.185, 0.188, 0.198, 0.205, 0.219, 0.236		
From (1) screened and/or examined to (3) heart attack with no treatment by initial dipstick test result, sex and age	<1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.005, 0.041, 0.076, 0.132, 0.126, 0.068	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.019, 0.078, 0.130, 0.234, 0.275, 0.372		
	≥1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.000, 0.000, 0.018, 0.033, 0.112, 0.077		
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.003, 0.010, 0.048, 0.079, 0.211, 0.224		
From (3) heart attack to (5) death by sex and age	1st year	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	2.8, 13.4, 13.0, 19.5, 33.7, 33.3	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	33.3, 0.0, 16.9, 25.0, 36.6, 45.8		
	2nd year	Male and female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	3.8, 3.8, 6.7, 19.5, 41.2, 100.0	±50	[24]
From (3) heart attack/(4) stroke to (2) ESRD				0.202	±50	[27]
From (1) screened and/or examined to (4) stroke with no treatment by initial dipstick test result, sex and age	<1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.026, 0.139, 0.264, 0.477, 0.738, 0.769	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.050, 0.202, 0.357, 0.655, 1.052, 1.540		
	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.014, 0.083, 0.124, 0.271, 0.508, 0.570			
	Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.034, 0.133, 0.187, 0.382, 0.699, 0.905			
From (4) stroke to (5) death by sex and age	1st year	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	19.1, 14.3, 9.9, 10.6, 12.7, 18.2	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	13.6, 14.0, 13.7, 6.8, 14.8, 18.1		
	2nd year	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85	6.8, 8.2, 9.5, 12.6, 16.6, 23.3, 37.6, 61.9, 95.1, 100.0	±50	Calculated from Suzuki et al. [25, 26]
		Female	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85	5.4, 6.4, 7.5, 9.0, 12.5, 18.4, 26.4, 40.1, 52.6, 71.7		



**Table 1** continued

			Base-case value	Range tested in sensitivity analysis (%)	Source
From (1) screened and/or examined to (5) death by sex and age	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, 95–99, 100	0.002, 0.003, 0.004, 0.007, 0.010, 0.015, 0.024, 0.042, 0.070, 0.119, 0.196, 0.284, 0.397	±50	[28]
	Female	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, 95–99, 100	0.001, 0.001, 0.002, 0.003, 0.004, 0.006, 0.010, 0.019, 0.036, 0.070, 0.132, 0.213, 0.327		
<i>Effectiveness of treatment (%)</i>					
Reduction of transition probabilities from (1) screened and/or examined to (2) ESRD with treatment of CKD			42.1	±50	[20]
Reduction of transition probabilities from (1) screened and/or examined to (3) heart attack with treatment of CKD			71.0	±50	[23]
Reduction of transition probabilities from (1) screened and/or examined to (4) stroke with treatment of CKD			69.3	±50	[23]
<i>Quality of life adjustment</i>					
<i>Utility weight</i>					
(1) Screened and/or examined	Stage 1, stage 2, stage 3, stage 4, stage 5		0.940, 0.918, 0.883, 0.839, 0.798	±20	[31]
(2) ESRD			0.658	±20	[32]
(3) Heart attack			0.771		
(4) Stroke			0.714		
<i>Costing</i>					
<i>Annual cost per person (¥)</i>					
Screening	Dipstick test only, serum Cr assay only, dipstick test and serum Cr		267, 138, 342	±50	Survey of health checkup service providers
Detailed examination			25,000	±50	Expert opinion
CKD treatment	Stage 1, stage 2, stage 3, stage 4, stage 5		120,000, 147,000, 337,000, 793,000, 988,000	±50	Expert opinion
ESRD treatment			6,000,000	±50	[33]
Heart attack treatment	1st year, 2nd year		2,780,000, 179,000	±50	[34]
Stroke treatment	1st year, 2nd year		1,000,000, 179,000	±50	[34]

Decision tree

Figure 1a shows our decision tree comparing a do-nothing scenario with a screening scenario. After the decision node, participants under the do-nothing scenario follow the Markov model shown in Fig. 1b. For those under the screening scenario, three types of screening test are considered: (a) dipstick test to check proteinuria only, (b) serum Cr assay only and (c) dipstick test and serum Cr assay. Other tests such as microalbuminuria and cystatin C [14] are not considered, because they are not available options in the context of this study.

Screened participants are portioned between CKD patients who undergo treatment and those who are left untreated through three chance nodes. The first chance node divides the participants between those who require further examination and those left untreated. Participants with (a) dipstick test only,  $\geq 1+$ ; with (b) serum Cr assay only,  $\geq$ stage 3; and with (c) dipstick test and serum Cr assay, either  $\geq 1+$  or  $\geq$ stage 3, are screened as requiring further examination. Those screened as requiring no further examination follow the Markov model. These are implemented by initial renal function stratum.

The second chance node divides participants screened as requiring further examination into those who seek detailed examination at health care providers and those who avoid any further examination. Its probability is assumed at 40.0% based on the literature [15, 16] and of the opinion of an expert committee set up for the purpose of this study, whose members are acknowledged in the “Acknowledgements” section. Those who avoid further examination follow the Markov model.

The third chance node divides participants who underwent further examination into those who undergo treatment

of CKD and those left untreated. We derived these probabilities by initial renal function stratum with a Delphi survey of the expert committee. Regarding the strata of stage 3 CKD, a cut-off value of eGFR ( $50 \text{ ml/min/1.73 m}^2$ ) and comorbidity such as hypertension, diabetes and/or hyperlipidaemia are considered in order to depict the difference in clinical practice when recommending start of treatment [17]. We label early stage 3 CKD and advanced stage 3 CKD according to this criterion. Among stage 3 CKD patients, the probability of falling into advanced stage 3 CKD by either eGFR  $< 50 \text{ ml/min/1.73 m}^2$  or having comorbidity is 83.5%, calculated from the Japan Tokutei-Kenshin CKD Cohort 2008. Each value is shown in Table 1. All participants follow the Markov model after their completion of detailed examination.

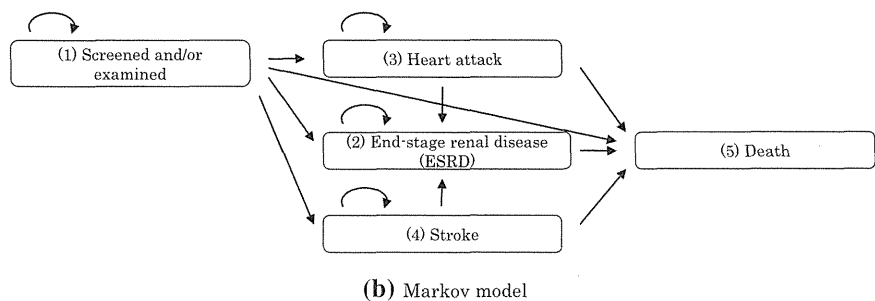
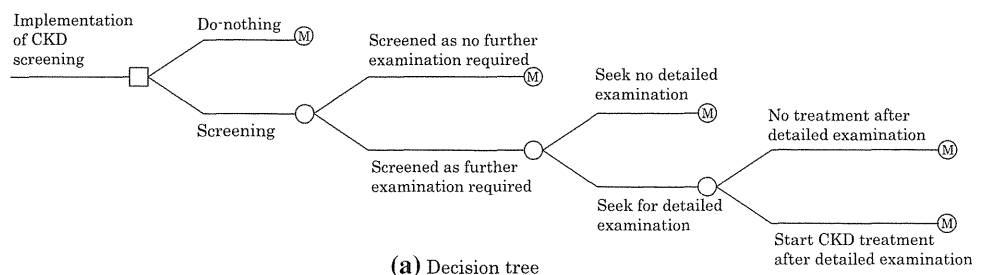
Markov model

The Markov model consists of five health states: (1) screened and/or examined, (2) ESRD, (3) heart attack, (4) stroke and (5) death. Transitions between these states are indicated by arrows. Although individuals follow various courses other than these five health states and indicated transitions, we model in this way based on available data and literature.

We set the span of staying in each state of the Markov model at 1 year. Annual transition probabilities from (1) screened and/or examined to (2) ESRD with no treatment by the initial renal function stratum are calculated from our database of screened cohort in Okinawa Prefecture [18] for this study, since there is no operational predictive model for progression of CKD to ESRD such as Tangri et al. [19] in Japan. Each value is shown in Table 1. Reductions of these transition probabilities brought about by treatment of CKD

Fig. 1 Economic model.

(M): Markov model



are set at 42.1% based on Omae et al. [20], who investigated the effectiveness of angiotensin-converting enzyme inhibitor in improving renal prognosis. This is a unique Japanese evidence of treatment effectiveness evaluating progression to ESRD which can be compared with our Okinawa cohort [18]. The subsequent transition probabilities to (5) death are calculated from the life expectancy of dialysis starters according to a complete count report of Japanese patients on dialysis [21] by sex and age. Each value is shown in Table 1.

Transition probabilities from (1) screened and/or examined to (3) heart attack with no treatment are adopted from an epidemiological study in Okinawa by Kimura et al. [22] by initial dipstick test result, age and sex. Each value is shown in Table 1. Reductions of these transition probabilities brought about by treatment of CKD are set at 71.0% based on the Hisayama study by Arima et al. [23]. The subsequent transition probabilities to (5) death are adopted from Kimura et al. [22] by age and sex for the first year, and from Fukiyama et al. [24] for the second year and thereafter. Each value is shown in Table 1.

Transition probabilities from (1) screened and/or examined to (4) stroke with no treatment are adopted from Kimura et al. [22] by initial dipstick test result, age and sex. Each value is shown in Table 1. Reductions of these transition probabilities brought about by treatment of CKD are set at 69.3% based on Arima et al. [23]. The subsequent transition probabilities to (5) death are adopted from Kimura et al. [22] by age and sex for the first year, and calculated from the Stroke Register in Akita of Suzuki [25, 26] for the second year and thereafter. Each value is shown in Table 1.

A transition probability from (3) heart attack and (4) stroke to (2) ESRD is adopted from an epidemiological study in Okinawa by Iseki et al. [27].

Transition probabilities from (1) screened and/or examined to (5) death are adopted from Vital Statistics of Japan 2008 [28] by age and sex. Each value is shown in Table 1.

We take a life-long time horizon so that the Markov cycle is repeated until each age stratum reaches 100 years old.

### Quality of life adjustment

In order to estimate outcomes, use of quality-adjusted life years (QALYs) is recommended for economic evaluation of health care [29, 30]. QALYs are calculated as the sum of adjusted life-years experienced by a patient, where the adjustment is made by multiplying time by weights linked to the changing health state of the patient. The quality-adjustment weight is a value between 1 (perfect health) and 0 (death), which is one of the health-related quality of life measurements. Regarding (1) screened and/or examined, weights are assigned according to CKD stage based on initial renal function, using values adopted from Tajima et al. [31]. Weights for (2) ESRD, (3) heart attack and (4)

stroke are cited from a past economic evaluation of anti-hypertensive treatment in Japanese context by Saito et al. [32].

### Costing

From the societal perspective, costing should cover the opportunity cost borne by various economic entities in society. In the context of this study, costs borne by social insurers and patients are considered, since the cost of SHC is borne by social insurers and the cost of treatment is shared by social insurers and patients in Japan's health system. The amount of direct payments to health care providers by these entities is estimated as costs, while costs of sector other than health and productivity losses are left uncounted in this study. Cost items are identified along the decision tree and Markov model: screening, detailed examination, treatment of CKD, treatment of ESRD, treatment of heart attack and treatment of stroke. Each value is shown in Table 1.

Costs of screening were surveyed in five prefectures by inquiring health checkup service providers' price of adding CKD screening test to a test package that does not include renal function tests. Average price of those for (a) dipstick test to check proteinuria only, (b) serum Cr assay only and (c) dipstick test and serum Cr assay was ¥267 (US \$3.0, with US \$1 = ¥90), ¥138 (US \$1.5) and ¥342 (US \$3.8) per person, respectively. Cost of detailed examination is set at ¥25,000 (US \$278) per person according to the national medical care fee schedule and a treatment model developed by the expert committee. Annual costs of CKD treatment per person are set at ¥120,000 (US \$1,333) for stage 1 CKD, ¥147,000 (US \$1,633) for stage 2 CKD, ¥337,000 (US \$3,744) for stage 3 CKD, ¥793,000 (US \$8,811) for stage 4 CKD and ¥988,000 (US \$10,978) for stage 5 CKD, also from the national medical care fee schedule and a treatment model developed by the expert committee. Annual cost of ESRD treatment per person, ¥6,000,000 (US \$66,667), is cited from a review of renal disease care in Japan by Fukuhara et al. [33]. Annual cost of heart attack treatment per person, ¥2,780,000 (US \$30,889) for the first year and ¥179,000 (US \$1,989) for subsequent years, are cited from a past economic evaluation of cardiovascular disease prevention in Japanese context by Tsutani et al. [34]. Similarly, annual costs of stroke treatment per person, ¥1,000,000 (US \$11,111) for the first year and ¥179,000 (US \$1,989) for subsequent years, are cited from Tsutani et al. [34] as well.

### Discounting

Both outcomes and costs are discounted at a rate of 3% [30].

## Policy options for economic evaluation

To draw significant policy implications from this economic evaluation, policy options from status quo need to be defined. Under the current SHC, the dipstick test to check proteinuria is mandatory, while serum Cr assay is not. However, some health insurers voluntarily provide serum Cr assay to participants in addition to SHC. We surveyed health insurers in five prefectures and found that 65.4% of them implement use of serum Cr assay. Also, we analysed the Japan Tokutei-Kenshin CKD Cohort 2008 and found that 57.3% of participants underwent use of serum Cr assay. Therefore, we define the status quo regarding screening test for CKD as 40% of insurers implementing dipstick test only and 60% implementing dipstick test and serum Cr assay.

Then we evaluate two policy options in this study: ‘Policy 1: Requiring serum Cr assay’, and ‘Policy 2: Requiring serum Cr assay and abandoning dipstick test’. Policy 1 means mandating use of serum Cr assay in addition to the currently used dipstick test, so that 100% of insurers implement both dipstick test and serum Cr assay if policy 1 is taken. Policy 2 is considered based on two recent health policy contexts. One is the discussion aroused during the development of SHC in which requiring serum Cr assay only and abandoning dipstick test used in the former occupational health checkup scheme attracted substantial support. It is expected that such a policy option will be proposed in the revision of SHC. Another relates to the change in diagnosis criterion of diabetes [35], in which a blood test to check the level of haemoglobin A1c instead of a dipstick test to check urinary sugar level has become pivotal. Implementing dipstick test for checking proteinuria only bears scrutiny from the viewpoint of economic evaluation. We assume that 100% of insurers would stop providing dipstick test if policy 2 is adopted.

We calculate incremental cost-effectiveness ratios (ICERs) for these two policy options using our economic model. ICER is a primary endpoint of cost-effectiveness analysis, which is defined as follows:

$$\text{ICER} = \frac{\text{Incremental cost}}{\text{Incremental effectiveness}} \\ = \frac{\text{Cost}_{\text{New policy}} - \text{Cost}_{\text{Status quo}}}{\text{Effectiveness}_{\text{New policy}} - \text{Effectiveness}_{\text{Status quo}}}$$

This means the additional cost required to gain one more QALY under new policy.

## Sensitivity analysis

Economic modelling is fundamentally an accumulation of assumptions adopted from diverse sources. Therefore, it is imperative to appraise the stability of the model. We

perform one-way sensitivity analyses for our model assumptions. Assumed probabilities about the participant cohort, the decision tree and the Markov model are changed by  $\pm 50\%$ . Reductions of transition probabilities brought about by treatment are also changed by  $\pm 50\%$ . Utility weights for quality of life adjustments are changed by  $\pm 20\%$ . Costs are changed by  $\pm 50\%$ . Discount rate is changed from 0% to 5%. We also changed our assumption about status quo that 40% of insurers implement dipstick test only and 60% implement dipstick test and serum Cr assay by  $\pm 50\%$  as well.

## Results

### Model estimators

Table 2 presents the model estimators. Under the do-nothing scenario, no patient is screened, with average cost of renal disease care per person of ¥2,125,490 (US \$23,617) during average survival of 16.11639 QALY. When (a) dipstick test to check proteinuria only is applied, 832 patients out of 100,000 participants are screened, with additional cost of ¥7,288 (US \$81) per person compared with the do-nothing scenario, for additional survival of 0.00639 QALY (2.332 quality-adjusted life days). When (b) serum Cr assay only is applied, 3,448 patients are screened with additional cost of ¥390,002 (US \$4,333) per person compared with the do-nothing scenario, for additional survival of 0.04801 QALY (17.523 quality-adjusted life days). When (c) dipstick test and serum Cr assay are applied, 3,898 patients are screened with additional cost of ¥395,655 (US \$4,396) per person compared with the do-nothing scenario, for additional survival of 0.04804 QALY (17.535 quality-adjusted life days).

Model estimators of ICERs were calculated as ¥1,139,399/QALY (US \$12,660/QALY) for (a) dipstick test only, ¥8,122,492/QALY (US \$90,250/QALY) for (b) serum Cr assay only and ¥8,235,431/QALY (US \$91,505/QALY) for (c) dipstick test and serum Cr assay.

### Cost-effectiveness

Table 3 presents the results of cost-effectiveness analysis. Regarding the status quo that 40% of insurers implement dipstick test only and 60% implement dipstick test and serum Cr assay, 2,837 patients out of 100,000 participants are screened, with average cost of screening and renal disease care per person of ¥2,365,798 (US \$212,922) during average survival of 16.14777 QALY. Taking policy 1 that 40% of insurers currently using dipstick test only start use of serum Cr assay screens more patients (3,898).

**Table 2** Model estimators

	No. of patients per 100,000 participants	Cost (¥)	Incremental cost (¥)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Incremental cost-effectiveness ratio (¥/QALY)
Do-nothing	0	2,125,490		16.11639		
(a) Dipstick test only	832	2,132,778	7,288	16.12278	0.00639	1,139,399
(b) Serum Cr assay only	3,448	2,515,492	390,002	16.16440	0.04801	8,122,492
(c) Dipstick test and serum Cr assay	3,898	2,521,145	395,655	16.16443	0.04804	8,235,431

**Table 3** Results of cost-effectiveness analysis

	No. of patients per 100,000 participants	Cost (¥)	Incremental cost (¥)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Incremental cost-effectiveness ratio (¥/QALY)
Status quo	2,837	2,365,798		16.14777		
Policy 1: requiring serum Cr assay	3,898	2,521,145	155,347	16.16443	0.01666	9,325,663
Policy 2: requiring serum Cr assay and abandoning dipstick test	3,448	2,515,492	149,694	16.16440	0.01663	9,001,414

It costs more, but it gains more. Its incremental cost is ¥155,347 (US \$1,726), and its incremental effectiveness is 0.01666 QALY (6.081 quality-adjusted life days), resulting in ICER of ¥9,325,663/QALY (US \$103,618/QALY). Taking policy 2 that 40% of insurers currently using dipstick test only start use of serum Cr assay and abandon dipstick test screens more patients (3,448) compared with the status quo as well. It also costs more, but it gains more. Its incremental cost is ¥149,694 (US \$1,663), and its incremental effectiveness is 0.01663 QALY (6.070 quality-adjusted life days), resulting in ICER of ¥9,001,414/QALY (US \$100,016/QALY).

#### Stability of cost-effectiveness

One-way sensitivity analyses produce similar results not only between policy 1 and policy 2 but also among three model estimators of ICER. Therefore, we present a tornado diagram of policy 1 as an example in Fig. 2. Ten variables with large change of ICER are depicted. A threshold to judge cost-effectiveness is also drawn, which is according to World Health Organization's (WHO) recommendation, being three times gross domestic product (GDP) per capita [36]. Its value is ¥11.5 million/QALY (US \$128 thousand/QALY) gain in 2009 in Japan.

The effectiveness of CKD treatment to delay progression to ESRD is found to be the most sensitive. Decreasing the effect by 50% increases ICER to ¥16,280,537/QALY (US \$180,895/QALY). The effectiveness of CKD treatment to prevent stroke is also found to be the 10th largest change of ICER, but its range is limited.

The cost of treatment for stage 5 CKD is found to be the second most sensitive. Increasing the cost by 50%

increases ICER to ¥14,404,335/QALY (US \$160,048/QALY). The cost of ESRD treatment is found to be the fifth largest change, and the change is in the opposite direction; decreasing this increases ICER. Another cost item depicted is the cost of treatment for stage 3 CKD, which is found to be the sixth largest change.

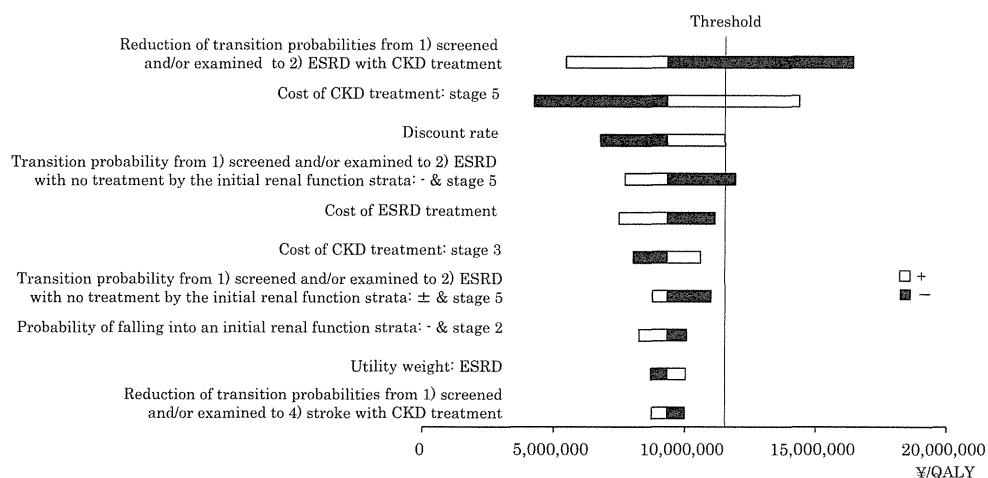
The discount rate is found to be the third most sensitive. Discounting at a rate of 5% makes ICER ¥11,373,185/QALY (US \$126,369/QALY). Since policy 1 can screen CKD patients without proteinuria by use of serum Cr assay, the prognosis of non-proteinuric stage 5 CKD without treatment is found sensitive as the fourth and the seventh largest change. The eighth largest change depicted relates to the prevalence of CKD in participating population, i.e. stage 2 CKD without proteinuria. The ninth largest change is utility weight for ESRD.

Taking the threshold to judge cost-effectiveness, one-way sensitivity analyses alter the interpretation of the results for only three variables: reductions of transition probabilities from (1) screened and/or examined to (2) ESRD with the treatment of CKD; cost of treatment for stage 5 CKD; and transition probability from (1) screened and/or examined to (2) ESRD with no treatment by initial renal function for stage 5 CKD without proteinuria.

#### Discussion

We conduct a cost-effectiveness analysis of CKD screening test in SHC. Facing the scheduled revision of mandatory test items, we appraise two possible policy options compared with the status quo that 40% of insurers implement dipstick test to check proteinuria only and 60% implement

**Fig. 2** Tornado diagram of policy 1. This tornado diagram shows ten variables which are found to be sensitive to the change in assumptions. Ten variables are presented, ordered according to the size of the change of ICER from top to bottom. The change of ICERs are represented by *white bars* when increasing the variable or by *black bars* when decreasing the variable from base-case value. The threshold to judge cost-effectiveness is  $3 \times$  GDP per capita (¥11.5 million/QALY gain)



dipstick test and serum Cr assay. Policy 1 is to mandate serum Cr assay in addition to the current dipstick test, so that 100% of insurers implement both dipstick test and serum Cr assay. Policy 2 is to mandate serum Cr assay and abandon dipstick test, so that 100% of insurers would stop providing dipstick test and switch to serum Cr assay. Our base-case analysis suggests that both policy options cost more and gain more. Estimated ICERs are ¥9,325,663/QALY (US \$103,618/QALY) for policy 1 and ¥9,001,414/QALY (US \$100,016/QALY) for policy 2.

To interpret these ICERs, there is no established value of social willingness to pay for one QALY gain in public health programmes such as mass screening in Japan, although some suggest ¥5 million/QALY (US \$56 thousand/QALY) for an innovative medical intervention [37]. We follow WHO recommendation in this study, which is three times GDP per capita [36]. Its value is ¥11.5 million/QALY (US \$128 thousand/QALY) gain in 2009 in Japan. Given this threshold, both policy 1 and policy 2 are judged as cost-effective. Therefore, mandating serum Cr assay in SHC can be justifiable as an efficient allocation of finite resources for health. Between policy 1 and policy 2, the ICER of policy 2 is slightly more favourable than that of policy 1, while 450 more patients out of 100,000 participants are screened by adopting policy 1. If secondary prevention of CKD is emphasised as a policy objective in addition to efficiency, policy 1 is an acceptable option as well as policy 2.

Our model estimators have a policy implication, although estimated ICERs do not directly depict any marginal change in society. The ICER of (a) dipstick test only compared with the do-nothing scenario, ¥1,139,399/QALY (US \$12,660/QALY), is remarkably favourable. This implies that mass screening with dipstick test only is cost-effective compared with abolishment of mass screening for kidney diseases altogether. Therefore, continuing the current policy, i.e. mandatory dipstick test, could be justifiable as an efficient resource allocation.

This contrasts with the reported cost-ineffectiveness of annual mass screening for adults using dipstick test to check proteinuria in the USA [12], although direct comparison cannot be made between the results of economic evaluations under different health systems. The difference could be attributable to the difference in the prevalence of proteinuria among screened population, with 5.450% being used in our model based on the Japan Tokutei-Kenshin CKD Cohort 2008, while 0.19% is assumed in the US study. Such epidemiological differences are known in terms of not only quantity but also in quality [7]. The prevalence of glomerulonephritis, especially IgA nephropathy, is higher in Asian countries including Japan compared with Western countries [10]. Also, the prevalence of renovascular disease such as ischaemic nephropathy, with which patients are often non-proteinuric until advanced stages of CKD, is lower in Asian countries [38]. The inclusion of heart attack and stroke into our model, which are excluded in the US model [12], may have also made the ICER more favourable.

There is a report of cost-ineffectiveness of population-based screening for CKD with serum Cr assay from Canada [39]. This Canadian model can be compared with our model estimators of (b) serum Cr only compared with the do-nothing scenario. Their health outcomes gain or incremental effectiveness is 0.0044 QALY, which is smaller than ours, 0.04801 QALY, while their incremental cost is C \$463 (US \$441, using US \$1 = C \$1.05), which is also smaller than ours, ¥390,002 (US \$4,333). These differences probably reflect the difference in the prevalence of CKD between Canada and Japan. Regarding the efficiency of screening programme, our model estimator of ICER, ¥8,122,492/QALY (US \$90,250/QALY), is slightly more favourable than that of Canada, C \$104,900/QALY (US \$99,905/QALY). However, the contradictory conclusion regarding cost-effectiveness is not due to this difference but rather the threshold taken. The Canadian study adopts lower value such

as C \$20,000 to C \$50,000/QALY (US \$19,048 to US \$47,619/QALY) following local practice [40].

Our sensitivity analysis suggests instability of the results in only three variables, so our findings are robust to a certain extent. The most sensitive variable is the effectiveness of CKD treatment delaying progression to ESRD: 42.1% reduction is adopted in our economic model according to the unique clinical evidence from Japan, whose agent is angiotensin-converting enzyme inhibitor. It is marginally larger than comparative values reported from Western countries. Reductions in the rate of GFR decline are 35.9% by Agodoa et al. [41], 39.8% by The GISEN Group [42] and 22.5% by Ruggenenti et al. [43]. However, we think our assumption of base-case value is reasonable in two accounts: in light of the indication of angiotensin receptor blockers [17], whose use is more tolerated than angiotensin-converting enzyme inhibitors [44], and the higher prevalence of glomerulonephritis including IgA nephropathy, being a primary renal disease for ESRD, in Japan [10], for which the effect of early treatment such as renin-angiotensin system (RAS) inhibition, an immunosuppression, reduces risk of ESRD by 60% [45].

In regards to the other sensitive variables, we think the prognosis of non-proteinuric stage 5 CKD without treatment does not greatly undermine our findings of base-case analysis, since the value is calculated from extended follow-up of an established database [18]. Uncertainty of the base-case value should be much less than the analysed  $\pm 50\%$ . On the other hand, the cost of treatment for stage 5 CKD relates to one of the weaknesses of this study, as discussed in the following.

There are weaknesses in this study. The most significant one is that our economic model depicts the prognosis of CKD by initial renal function stratum. This approach is taken because of the limitation of epidemiological data, and it has little difficulty in estimating outcomes in terms of survival. However, it becomes problematic when it comes to costing. For example, a patient initially screened as stage 1 CKD stays at (1) screened and/or examined before transiting to the following health states such as (2) ESRD. This means that a patient skips over stage 2 CKD to 5 CKD before progressing to ESRD. To estimate the cost for this health state, the diversity of patients in terms of progression of the CKD stages should be taken into account. Our expert committee has developed treatment models to understand this problem. This type of uncertainty is larger in stage 1 CKD and smaller in stage 5 CKD, but the cost of stages 1–4 CKD are not found to be so sensitive in our sensitivity analysis. Also, we think that uncertainty of the cost of stage 5 CKD, the second most sensitive variable, is less than the analysed  $\pm 50\%$ , and our findings based on the base-case analysis are plausible. The problem

**Table 4** Recommendation of the Japanese Society of Nephrology Task Force for the validation of urine examination as a universal screening

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Mandate use of serum Cr assay in addition to the current dipstick test in the next revision of SHC

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also affects quality of life adjustment, which tends to produce larger QALY outcomes.

Other weaknesses include our assumption of 100% adherence to treatment and so on. However, the most significant strength of this study is that our economic model depends totally on evidence from Japan only, which could justify our simplification in modelling on data availability basis. There is an opportunity for further refinement of our economic model, because a large-scale field trial evaluating the effect of multifactorial treatment including lifestyle modification for early-stage CKD [46] is ongoing in Japan, which will enable us to model progression of CKD with more rigorous clinical evidence [47].

In conclusion, we, the Japanese Society of Nephrology Task Force for the Validation of Urine Examination as a Universal Screening, recommend to mandate use of serum Cr assay in addition to the current dipstick test in the next revision of SHC, from the viewpoint of value for money and the importance of secondary prevention (Table 4). We think that continuation of current policy, in which dipstick test only is mandatory, is still a sensible policy option. Development of adequate Specific Counselling Guidance for screened participants is also recommended.

Whereas the primary objective of this study is to appraise policy options in Japanese context, it also demonstrates that good value for money can be expected from mass screening with dipstick test to check proteinuria in population with high prevalence; that is, a population strategy could be adopted for control of CKD. However, caution is needed when extrapolating this conclusion, since the scope of costing of our economic model does not cover the initial cost of launching mass screening. The model here is based on currently running SHC. The practice of annual mass screening for adults in Japan is quite exceptional, while such universal programmes are rarely found in other countries [48].

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**Conflict of interest** The authors have declared that no conflicts of interest exist.

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Original Article

## Glomerular hyperfiltration in prediabetes and prehypertension

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### Abstract

**Background.** This study aimed to investigate the associations of hyperfiltration and hypofiltration with prediabetes and prehypertension.

**Methods.** The study subjects included 99 140 people aged 20–89 years who underwent health checkups in Aichi Prefecture, Japan. The prevalence of hyperfiltration [estimated glomerular filtration rate (eGFR) above the age-/sex-specific 95th percentile] and hypofiltration (eGFR below the age-/sex-specific 5th percentile) was compared among stages of prediabetes (fasting plasma glucose <100, 100–109, 110–125 and  $\geq$ 126 mg/dL for no prediabetes, Stage 1 prediabetes, Stage 2 prediabetes and diabetes, respectively) and prehypertension [blood pressure (BP) <120/80, 120–129/80–84, 130–139/85–89 and  $\geq$ 140/90 mmHg for no prehypertension, Stage 1 prehypertension, Stage 2 prehypertension and hypertension, respectively].

**Results.** The prevalence of hyperfiltration increased with increasing stage of prediabetes [odds ratios (ORs): 1.29, 1.58 and 2.47 for Stage 1 prediabetes, Stage 2 prediabetes and diabetes, respectively] and prehypertension (ORs: 1.10, 1.33 and 1.52 for Stage 1 prehypertension, Stage 2 prehypertension and hypertension, respectively). Hypofiltration was not associated with prediabetes or prehypertension.

**Conclusions.** The prevalence of glomerular hyperfiltration increased with increasing stages of prediabetes and prehypertension. Therefore, kidney function should be monitored in subjects with prediabetes or prehypertension. In subjects with hyperfiltration, earlier treatment of hyperglycemia and high BP may be necessary to prevent the development of kidney damage.

**Keywords:** glomerular hyperfiltration; prediabetes; prehypertension

### Introduction

Glomerular hyperfiltration is well-recognized as an early renal alteration in subjects with diabetes and hypertension [1, 2], and it may be a marker for subsequent kidney dam-

age characteristic of hypofiltration in chronic kidney disease (CKD) and end-stage renal disease (ESRD) [3–7]. However, it is unclear whether hyperfiltration occurs in the early stages of hyperglycemia and high blood pressure (BP), such as in prediabetes and prehypertension [8, 9]. Because hyperfiltration is considered to represent an early and reversible stage of kidney damage [7], identifying subjects at increased risk for CKD/ESRD among those with prediabetes/prehypertension by identifying individuals with hyperfiltration may be an important and effective preventative strategy.

However, so far, there are no widely accepted definitions for hyperfiltration [10]. Using fixed reference values, many young subjects are defined as having hyperfiltration, reflecting the decline in glomerular filtration rate (GFR) with age. The same problem occurs for hypofiltration because many older subjects are defined as having CKD, even though their risk for this disease may not be high [11]. Thus, age- and sex-specific reference values for hyperfiltration and hypofiltration are needed.

Therefore, the objectives of this study were to (i) determine reference values for hyperfiltration and hypofiltration according to age and sex in subjects without prediabetes or prehypertension and (ii) investigate the associations of hyperfiltration and hypofiltration with prediabetes and prehypertension.

### Materials and methods

#### Study population

The Aichi CKD Epidemiology Conference was initiated in 2008 with the support of the Aichi Kidney Foundation for the purpose of surveying the prevalence of CKD in Aichi prefecture, Japan. Four large-scale community- or bureau-based health-check centers in Okazaki, Hekinan and Kasugai Cities and Chita County in Aichi prefecture were invited to enroll in this study. The centers provided data for participants who enrolled in their health checkup programs conducted between April 2006 and March 2008. The latest data for each participant were used. Subjects aged 20–89 years with complete data for the following characteristics were included in this study: serum creatinine, age, sex, systolic/diastolic BP and fasting plasma glucose (FPG). This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

### Estimation of the GFR

Serum creatinine (SCr) was measured in all participants using an enzymatic method. The method used to measure SCr was initially calibrated at the Central Laboratory in Aichi prefecture for all four centers, and their precision and accuracy were authorized by the Japanese Association of Medical Technologists. The GFR of each participant was estimated from the SCr value, using the modified Modification of Diet in Renal Disease (MDRD) equation (adapted for Japanese by the Japanese Society of Nephrology [12]), as follows:

$$\begin{aligned} \text{Estimated GFR (eGFR) (mL/min/1.73m}^2\text{)} \\ = 194 \times \text{SCr}^{-1.094} (\text{mg/dL}) \times \text{age}^{-0.287} (\text{years}) (\times 0.739 \text{ if female}). \end{aligned}$$

### Definition of hyperfiltration and hypofiltration in healthy subjects

The distributions of eGFR in subjects without prediabetes (FPG < 100 mg/dL) and prehypertension (BP < 120/80 mmHg) were divided into 10-year age groups. Subjects being treated for diabetes, hypertension, kidney diseases and cancer and those with proteinuria (urinary protein  $\geq 1+$  on dipstick test) were excluded. The number of subjects aged  $\geq 80$  years was too small to derive reference values, so they were combined with those aged  $\geq 70$  years. Hyperfiltration was defined as eGFR above the age- and sex-specific 95th percentile for healthy subjects, while hypofiltration was defined as eGFR below the 5th percentile.

### Prevalence of hyperfiltration and hypofiltration according to the stages of prediabetes and prehypertension

Using the reference values determined as above, all of the participants were divided according to their eGFR as showing hyperfiltration, normal filtration and hypofiltration. The characteristics of the subjects were compared between those with hyperfiltration/hypofiltration and normal filtration. The prevalence of hyperfiltration and hypofiltration was also compared according to the stages of prediabetes and prehypertension [8, 9]. Subjects were categorized as having normal fasting glucose (i.e. no prediabetes; FPG < 100 mg/dL), Stage 1 prediabetes (FPG 100–109 mg/dL), Stage 2 prediabetes (FPG 110–125 mg/dL) or diabetes (FPG  $\geq 126$  mg/dL or under treatment for diabetes). Subjects were also categorized as having normal BP (i.e. no prehypertension; BP < 120/80 mmHg), Stage 1 prehypertension (BP 120–129/80–84 mmHg), Stage 2 prehypertension (BP 130–139/85–89 mmHg) or hypertension (BP  $\geq 140/90$  mmHg or under treatment for hypertension).

### Statistical analysis

Odds ratios (ORs) and 95% confidence intervals were estimated for hyperfiltration and hypofiltration using unconditional logistic regression analysis adjusted for age and sex (adjusted ORs) and for age, sex, body mass index, high-density lipoprotein cholesterol (HDL-C), lipid-lowering medication use, uric acid and smoking status. The analyses of stages of pre-

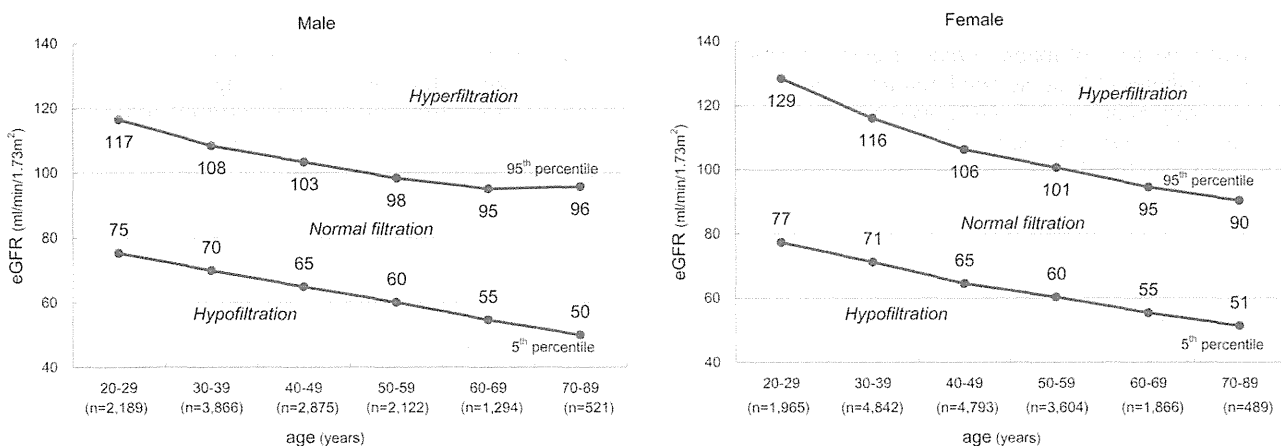
diabetes were also adjusted for systolic BP and anti-hypertensive medication use, while analyses of stages of prehypertension were also adjusted for FPG and glucose-lowering medication use as the stages of prediabetes and prehypertension were confounding (fully adjusted ORs). Proteinuria was not adjusted in the analysis because proteinuria is not just a confounder to be adjusted but the outcome (kidney damage) itself. The P-values for trends were calculated using a score variable assigning 0, 1, 2 and 3 for no prediabetes, Stage 1 prediabetes, Stage 2 prediabetes and diabetes (or for no prehypertension, Stage 1 prehypertension, Stage 2 prehypertension and hypertension).  $P < 0.05$  was considered statistically significant. All analyses were carried out using STATA version 9 software (StataCorp, College Station, TX).

## Results

A total of 99 140 people (54 547 males and 44 593 females) aged 20–89 years participated in this study. The distribution of eGFR and the reference values for hyperfiltration/hypofiltration in subjects without prediabetes or prehypertension ( $n = 30\,426$ ) for each 10-year age group are shown in Figure 1. Among those aged 50–59 years, the reference values for hyperfiltration and hypofiltration were  $\sim 100$  and 60 mL/min/1.73m<sup>2</sup>, respectively, for both sexes.

The characteristics of subjects according to filtration status are shown in Table 1. We found no clinically important differences between subjects with hyperfiltration and those with normal filtration except for fasting blood glucose level, while more of the subjects with hypofiltration were older males with higher uric acid, dyslipidemia and proteinuria, as compared with subjects with normal filtration.

Table 2 shows the prevalence of hyperfiltration and hypofiltration according to the stages of prediabetes and prehypertension. The prevalence of hyperfiltration increased with increasing stage of prediabetes (ORs: 1.29, 1.58 and 2.47 for Stage 1 prediabetes, Stage 2 prediabetes and diabetes, respectively;  $P$  for trend:  $< 0.001$ ) and stage of prehypertension (ORs: 1.10, 1.33 and 1.52 for Stage 1 prehypertension, Stage 2 prehypertension and hypertension, respectively;  $P$  for trend:  $< 0.001$ ). We found no association between hypofiltration and prediabetes or prehypertension, as the age- and sex-adjusted ORs were almost 1.00. Furthermore, hypofiltration was only weakly associated with diabetes and hypertension.



**Fig. 1.** Distribution of eGFR in subjects without prediabetes or prehypertension by sex and age ( $n = 30\,426$ ). The 95th and 5th percentiles are shown in 10-year age groups. Subjects with prediabetes (FPG  $\geq 100$  mg/dL), prehypertension (BP  $\geq 120/80$  mmHg), confirmed proteinuria (urinary protein  $\geq 1+$  on dipstick test) or being treated for diabetes, hypertension, renal diseases or cancer were excluded from this analysis. Hyperfiltration was defined as an eGFR over the age- and sex-specific 95th percentile and hypofiltration was defined as an eGFR below the 5th percentile.

**Table 1.** Characteristics of subjects with hyperfiltration/hypofiltration compared with subjects with normal filtration ( $N = 99\ 140$ )

	Normal filtration ( $n = 87\ 251$ )	Hyperfiltration ( $n = 5548$ )	Hypofiltration ( $n = 6341$ )
Age (years)	50.5 $\pm$ 15.1	51.4 $\pm$ 14.8	55.0 $\pm$ 16.0
Female	39 455 (45.2%)	2531 (45.6%)	2607 (41.1%)
Body mass index	22.63 $\pm$ 3.28	22.41 $\pm$ 3.65	23.28 $\pm$ 3.32
FPG (mg/dL) <sup>a</sup>	94.7 $\pm$ 15.6	100.9 $\pm$ 30.6	95.2 $\pm$ 15.1
HbA1c (%) <sup>a</sup>	5.17 $\pm$ 0.47	5.30 $\pm$ 0.92	5.22 $\pm$ 0.44
Glucose-lowering medication	3116 (3.6%)	400 (7.2%)	416 (6.6%)
Systolic BP (mmHg) <sup>b</sup>	122.1 $\pm$ 15.9	123.8 $\pm$ 16.6	123.2 $\pm$ 17.0
Diastolic BP (mmHg) <sup>b</sup>	74.4 $\pm$ 10.4	74.5 $\pm$ 10.7	75.5 $\pm$ 11.0
Anti-hypertensive medication	11 698 (13.4%)	830 (15.0%)	1667 (26.3%)
HDL-C (mg/dL) <sup>c</sup>	67.4 $\pm$ 17.8	67.7 $\pm$ 17.9	64.8 $\pm$ 18.4
Triglycerides (g/dL) <sup>c</sup>	88 (61–129)	87 (61–128)	100 (69–145)
Lipid-lowering medication	5841 (7.7%)	337 (6.6%)	730 (12.7%)
Uric acid (mg/dL)	5.29 $\pm$ 1.37	4.77 $\pm$ 1.33	6.15 $\pm$ 1.53
Proteinuria	3367 (3.9%)	270 (4.9%)	812 (12.9%)
Ever smokers	34 843 (39.9%)	2360 (42.5%)	2354 (37.1%)

<sup>a</sup>Subjects taking glucose-lowering medication are excluded.

<sup>b</sup>Subjects taking anti-hypertensive medication are excluded.

<sup>c</sup>Subjects taking lipid-lowering medication are excluded. Data are mean  $\pm$  SD, number (%) or median (interquartile range) for triglycerides. Hyperfiltration was defined as an eGFR over the age- and sex-specific 95th percentile and hypofiltration was defined as an eGFR below the 5th percentile as shown in Figure 1.

## Discussion

We found that the prevalence of hyperfiltration increased with increasing stages (i.e. worsening) of prediabetes and prehypertension. This suggests that renal function should be monitored in people with prediabetes or prehypertension to identify those with hyperfiltration who might be at increased risk for subsequent kidney damage.

Glomerular hyperfiltration is a well-recognized early renal change in subjects with diabetes and hypertension [1, 2], partly because of inappropriate afferent arteriole dilatation in diabetes [13] or elevated glomerular hydraulic pressure in hypertension [5]. GFR was reported to decrease significantly faster in subjects with hyperfiltration [1], and long-standing hyperfiltration may contribute to the development of kidney damage [3, 4]. Kidney failure may occur in people having had hyperfiltration for 30 years [5] because of progressive glomerular sclerosis that occurs as a result of prolonged glomerular hyperfiltration [6]. Preventing glomerular hyperfiltration can reduce glomerular injury [7].

New designations for prediabetes (impaired fasting glucose or impaired glucose tolerance) and prehypertension were recently introduced [8, 9]. Subjects with prediabetes and prehypertension are at increased risk for the development of CKD [14, 15] and ESRD [16, 17]. As a large proportion of the population has prediabetes and prehypertension (20 and 37% in our study), identifying subjects at

increased risk for CKD/ESRD among those with prediabetes or prehypertension by finding those with hyperfiltration may represent a beneficial and effective preventative strategy.

We found significant associations between hyperfiltration and prediabetes or prehypertension in a large population of subjects. To our knowledge, the only other study to have shown an association between hyperfiltration and prediabetes contained a small number of subjects with prediabetes ( $n = 24$ ) [18]. On the other hand, we are aware of no studies describing an association between hyperfiltration and prehypertension. Thus, this study is the largest study to date to show associations of hyperfiltration with prediabetes and prehypertension.

Interestingly, we found no association between hypofiltration and prediabetes or prehypertension. It is possible that prediabetes and prehypertension are associated with earlier stages of kidney damage (i.e. glomerular hyperfiltration), while long-term diabetes and hypertension are associated with hypofiltration and CKD. The finding that diabetes and hypertension were significantly associated with hypofiltration, whereas prediabetes and prehypertension were not, supports this hypothesis. Curhan [19] proposed the term ‘pre-CKD’ for low levels of albuminuria, and we suppose that hyperfiltration could represent pre-CKD, an early and reversible stage of kidney damage. Current guidelines recommend that prehypertension in subjects with CKD should be treated to achieve a target BP of <130/80 mmHg [9]. Treating high BP much earlier may stop the progression of nephropathy [20]. We suggest that hyperglycemia and high BP in people with hyperfiltration should be treated earlier to prevent the progression of renal dysfunction to CKD and ESRD.

There is no generally accepted definition for hyperfiltration [10]. In our study, we determined age- and sex-specific reference values for hyperfiltration and hypofiltration using a large presumably healthy population. We used the upper 95th and lower 5th percentiles rather than the mean  $\pm$  2 SD because eGFR is not normally distributed and because hyperfiltration and hypofiltration represent different disease conditions. Although the subjects with hyperfiltration in our study had lower eGFRs (being  $\sim$ 100 mL/min/1.73m<sup>2</sup> for people aged 50–59 years) compared with the subjects in former studies [10, 18], the prevalence of prediabetes and prehypertension was higher in our subjects. Thus, eGFR reference values for each sex and age group should be established for clinical use, particularly for older subjects. Hyperfiltration was prevalent in younger subjects followed by a higher prevalence of hypofiltration at an older age in diabetic subjects (23 and 0% in age 20s, and 7 and 13% in age 70s for prevalence of hyperfiltration and hypofiltration, respectively). This distribution is in accordance with the hyperfiltration hypothesis [5]. The Japanese eGFR equation can be used to identify people with hyperfiltration because the Japanese eGFR equation is more accurate than the MDRD Study equation, particularly for hyperfiltration [12, 21].

One limitation of our study is that we lack information on microalbuminuria and glucose tolerance following an oral glucose challenge. Thus, only impaired fasting glucose, but not impaired glucose tolerance, was used as a criterion for prediabetes. Microalbuminuria is another marker of early