Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study

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The purpose of this study was to explore risk factors affecting the incidence of chronic kidney disease (CKD) in general population. We conducted a 10-year follow-up study with 123 764 (male: 41 012, female: 82 752) adults aged 40 years and over who received community-based annual examinations. The primary outcome for the analysis was the development of CKD during the follow-up period. Predictors for the development of CKD were obtained by the significant hazard ratios (HR) in Cox regression model by sex. During the follow-up period, 4307 subjects (male: 2048, female: 2259) developed CKD stage I or II, and 19 411 subjects (male: 4257, female: 15 154) developed CKD stage III or higher. The baseline-adjusted predictor of developing CKD included age, glomerular filtration rate, hematuria, hypertension, diabetes, serum lipids, obesity, smoking status, and consumption of alcohol. Treated diabetes in male subjects, and treated hypertension, systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg, diabetes, and treated diabetes in female subjects were associated with more than a doubling of the HR. For the development of CKD stage III or higher, proteinuria of $\geqslant ++$, and proteinuria and hematuria were associated with more than a doubling of the HR in male subjects. The prevalence of newly developed CKD over 10 years was 23 718 subjects (19.2%) in adults. This study suggested that not only hypertension and diabetes but also several metabolic abnormalities were independent risk factors for developing CKD.

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The number of the patients with end-stage renal diseases (ESRD) has increased by about 9% per year in the USA, about 4% per year in most of European countries,[1] and about 7% per year in Japan.[2] The increased incidence of ESRD is recognized as a major public health problem worldwide. To prevent an increase in the number of ESRD patients in Japan, a dipstick urine examination has been available annually for every school child since 1973, for every working adult since 1972, and for every resident older than 40 years of age since 1982 under the auspices of local governments and the Ministry of Health, Labor and Welfare of Japan. Also, an annual measurement of serum creatinine was started in 1992 for every resident older than 40 years of age.[3,4] However, there have been few reports concerning the effects and outcomes of this screening program. In 2002, the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) gave a definition and classification system for chronic kidney disease (CKD).[5] The definition and classification of CKD were accepted by the international board of directors of Kidney Disease: Improving Global Outcomes (KDIGO).[6] CKD was defined in five stages, based on the appearance of proteinuria and glomerular filtration rate (GFR) levels. To estimate GFR, the modification of diet in renal disease (MDRD) formula was recommended for its accuracy in elderly subjects.[7] It was estimated that of the 19.2 million US adults with CKD, patients with early-stage CKD had no symptoms and the majority of individuals in early stage of CKD had gone undiagnosed even in developed countries.[8] Furthermore, patients with CKD have an increased risk of not only ESRD, but also poor cardiovascular outcomes and death.[9–11] A vast number of those with moderate CKD die before they develop more advanced CKD.[12]

In this study, we used mass screening data from a community-based annual health-check held in Ibaraki prefecture, Japan. We measured the prevalence of CKD and its yearly changes in subjects who were continuously

monitored over 10 years. From this study, we found the yearly incidence of CKD in a large community-based population older than 40 years, and tried to find risk factors for the development of CKD among the subjects during the 10-year follow-up period. Based on our results, strategies for effective methods to prevent the development of CKD among the general population could be devised.

RESULTS

Followed-up subjects

The age distribution of the subjects is shown in Figure 1. Table 1 shows baseline characteristics of the follow-up subjects. Male subjects were older, more frequently had diabetes, were hypertensive, and had smoking and drinking habits, whereas female subjects often had hematuria. A lower number of male subjects was observed in this study because most male residents under 60 years did not receive their annual physical checks at community centers, but at their work places.

Incidence of CKD stage I or II

During the follow-up period, 4307 subjects (male: 2048, female: 2259) developed CKD stage I or II. The incidence of developing proteinuria also increased with age (Figure 2). Male subjects developed CKD I or II more frequently than female subjects. The predictors of developing proteinuria included age, hematuria, hypertension, impaired glucose tolerance (IGT), diabetes, serum lipids, obesity, smoking status, and consumption of alcohol (inverse relationship) (Table 2). Baseline-adjusted predictors of developing proteinuria included treated hypertension (hazard ratio (HR), 2.28; 95% confidence interval (CI), 2.07–2.52) in female subjects, systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg (HR, 2.17; 95% CI, 1.85–2.54) in female subjects, and treated diabetes (HR, 2.48; 95% CI, 2.12–2.91 in male subjects; HR, 2.91; 95% CI, 2.46–3.45 in female subjects), which were associated with more than a doubling of the HR of developing proteinuria. The HR of developing proteinuria increased with elevations in blood pressure levels in both genders. In the subjects with hypercholesterolemia, low high-density lipoprotein cholesterol (HDL-C), and hypertriglyceridemia, the HR of developing proteinuria increased in both genders. Obesity

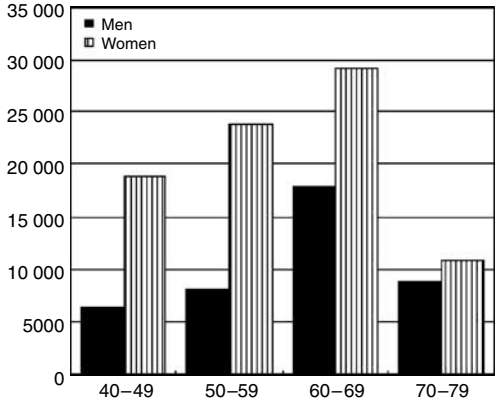

Figure 1 | Age distribution of the subjects. A lower number of male subjects under 60 years was observed in this study.

Table 1 | Baseline characteristics of the followed up subjects by sex

	Male (*n*=41 012)		Female (*n*=82 752)	
	Values	s.d. or %	Values	s.d. or %
Mean age, s.d.	61.8	10.2	58.3	10.0
Creatinine (mg/dl), s.d.	1.0	0.1	0.8	0.1
Estimated GFR (ml/min/1.73 m^2), s.d.	81.9	14.5	79.8	14.2
Proteninuria, *n*, %	638	1.6	521	0.6
Proteninuria and hematuria, *n*, %	248	0.6	399	0.5
Hematuria alone, *n*, %	3424	8.3	15 443	18.7
Hypertension, *n*, %	20 569	50.2	31 695	38.3
Treated hypertension, *n*, % among hypertensive subjects	8613	41.9	15 609	49.2
Impaired glucose tolerance *n*, %	6046	14.7	6998	8.5
Diabetes, *n*, %	3007	7.3	3329	4.0
Diabetes, with medication, *n*, % among diabetic subjects	1468	48.8	1769	53.1
Total cholesterol (mg/dl), s.d.	193	33.5	210	34.7
HDL-C (mg/dl), s.d.	52.5	14.7	56.8	14.1
Triglyceride (mg/dl), s.d.	147.3	94.4	136.5	78.6
Body mass index (kg/m^2), s.d.	23.2	2.9	23.5	3.2
Smoking				
Current, *n*, %	19 372	47.2	3437	4.2
Previous, *n* %	12 104	29.5	441	0.5
Alcohol consumption				
Occasional *n*, %	5223	12.7	4813	5.8
Ethanol <20 g/day, *n*, %	19 168	46.7	2944	3.6
Ethanol >20 g/day, *n*,%	2552	6.2	80	0.1

GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol.

increased the HR of developing proteinuria by 42% in male subjects and 56% in female subjects, and current smoking increased the HR by 26% in male subjects and 40% in female subjects. Alcohol consumption of less than 20 g/day decreased the HR of developing proteinuria, but this effect was diminished by consumption of alcohol of more than 20 g/day.

Figure 3 shows the trend of annual incidence of CKD I or II among the follow-up subjects. In the early years of follow-up, a higher incidence of developing proteinuria was observed. Subjects with trace proteinuria often developed apparent CKD I or II in the early years. However, after 1998, the trend of annual incidence of CKD I or II was about 0.4% per year in male subjects and about 0.2% per year in female subjects.

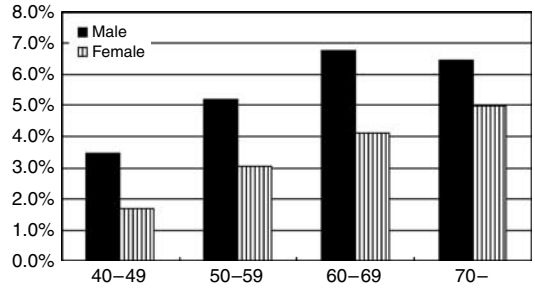

Figure 2 | Age-specific incidence rate of CKD stage I or II by sex. During the follow-up period, 4307 (male: 2048, female: 2259) developed CKD stage I or II. The incidence of developing proteinuria also increased with age. Male subjects more frequently developed CKD I or II than female subjects.

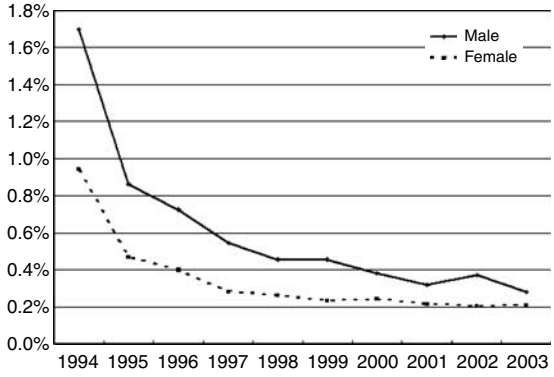

Figure 3 | Trend of annual incidence rate of CKD stage I or stage II by sex. In the early years of follow-up, a higher incidence of developing proteinuria was observed. Subjects with trace proteinuria often developed apparent CKD I or II in the early years. However, after 1998, the yearly incidence of CKD I or II was about 0.4% for male subjects and about 0.2% for female subjects.

Table 2 | The predictors for developing CKD stage I or II during 10-year follow-up period

	Male			Female		
Predictors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	1.02	1.02–1.03	<0.0001*	1.03	1.03–1.04	<0.0001*
GFR	0.99	0.99–1.00	0.0005*	1.00	1.00–1.01	0.1401
Hematuria (−)	1.00			1.00		
Hematuria (+)	1.24	1.04–1.47	0.0142*	1.30	1.16–1.46	<0.0001*
Hematuria >++	1.66	1.39–1.99	<0.0001*	1.60	1.43–1.79	<0.0001*
BP −140/−90 mm Hg	1.00			1.00		
BP 140–150/90–95 mm Hg	1.21	1.08–1.35	0.0008*	1.51	1.34–1.69	<0.0001*
BP 150–160/95–100 mm Hg	1.44	1.24–1.67	<0.0001*	1.67	1.45–1.93	<0.0001*
BP 160+/100+ mm Hg	1.73	1.48–2.02	<0.0001*	2.17	1.85–2.54	<0.0001*
Treated hypertension	1.85	1.66–2.07	<0.0001*	2.28	2.07–2.52	<0.0001*
IGT (−)	1.00			1.00		
IGT (+)	1.21	1.08–1.35	0.0011*	1.19	1.05–1.35	0.0055*
Diabetes (−)	1.00			1.00		
Diabetes (+)	1.76	1.47–2.11	<0.0001*	2.14	1.75–2.63	<0.0001*
Treated diabetes	2.48	2.12–2.91	<0.0001*	2.91	2.46–3.45	<0.0001*
Hypercholesterolemia (−)	1.00			1.00		
Hypercholesterolemia (+)	1.13	1.02–1.25	0.0225*	1.13	1.04–1.22	0.0025*
Low HDL-C (−)	1.00			1.00		
Low HDL-C (+)	1.14	1.02–1.27	0.0184*	1.17	1.03–1.32	0.0122*
Hypertriglyceridemia (−)	1.00			1.00		
Hypertriglyceridemia (+)	1.12	1.02–1.23	0.0134*	1.20	1.10–1.31	<0.0001*
Obesity (−)	1.00			1.00		
Obesity (+)	1.42	1.29–1.55	<0.0001*	1.56	1.44–1.69	<0.0001*
Never smoking	1.00			1.00		
Previous smoking	1.05	0.93–1.17	0.4486	1.54	0.98–2.42	0.0617
Current smoking	1.26	1.14–1.41	<0.0001*	1.40	1.16–1.69	0.0005*
Never drinker	1.00			1.00		
Occasional drinker	1.03	0.90–1.17	0.6577	0.96	0.80–1.14	0.637
Ethanol <20 g/day	0.86	0.78–0.95	0.002*	0.80	0.63–1.02	0.0685
Ethanol >20 g/day	1.04	0.86–1.25	0.5057	1.05	0.26–4.24	0.9444

BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IGT, impaired glucose tolerance.
*$P<0.05$.

Incidence of CKD stage III or higher

During the follow-up period, 19 411 subjects (male: 4257, female: 15 154) exhibited GFR < 60 ml/min/1.73 m^2. The incidence of CKD stage III or higher increased with age (Figure 4). The predictors of developing CKD stage III or higher were age, proteinuria, hematuria, hypertension, treated diabetes, and smoking status. Baseline-adjusted predictors of developing CKD stage III or higher included proteinuria (≥ + +) (HR, 2.26; 95% CI, 1.71–2.99), concomitant proteinuria, and hematuria (HR, 2.32; 95% CI, 1.81–2.97) in male subjects, which were associated with more than a doubling of the HR. Treated hypertension increased the HR of developing renal failure by 39%, and treated diabetes increased the HR by 20%; however, alcohol consumption of less than 20 g/day decreased the HR of developing CKD stage III or higher by 8% in male subjects and 9% in female subjects. Treated hypertension increased the HR of developing CKD stage III or higher by 39% (20% in female), and taking diabetes medication increased the HR by 20% in male subjects and 12% in female subjects. A reduced risk for developing CKD stage III in IGT or diabetes was observed (Table 3).

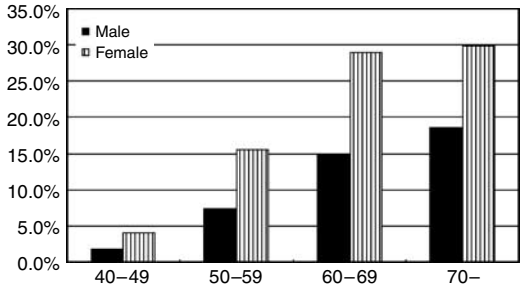

Figure 4 | Age-specific incidence rate of CKD stage III or higher by sex. During the follow-up period, 19 411 (male: 4257, female: 15 154) exhibited GFR < 60 ml/min/1.73 m^2. The incidence of CKD stage III or higher increased with age.

Figure 5 shows the yearly incidence of CKD stage III or higher among the follow-up subjects. In the early years of follow-up, a higher incidence of developing CKD stage III or higher was also observed. However, after 1998, the yearly incidence of CKD stage III or higher was about 0.8% per year in male subjects and about 1.5% per year in female subjects.

Table 3 | The predictors for developing CKD stage III or higher during 10-year follow-up period

	Male			Female		
Predictors	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.03	1.03–1.04	<0.0001*	1.05	1.05–1.06	<0.0001*
GFR	0.87	0.87–0.88	<0.0001*	0.90	0.89–0.90	<0.0001*
Proteinuria (−)	1.00			1.00		
Proteinuria (+)	1.66	1.34–2.07	<0.0001*	1.36	1.10–1.69	0.0046*
Proteinuria > ++	2.26	1.71–2.99	<0.0001*	1.78	1.37–2.30	<0.0001*
Proteinuria and hematuria	2.32	1.81–2.97	<0.0001*	1.43	1.18–1.73	0.0003*
Hematuria (−)	1.00			1.00		
Hematuria (+)	1.23	1.10–1.39	0.0004*	1.07	1.02–1.13	0.0043*
Hematuria > ++	1.31	1.15–1.50	<0.0001*	1.07	1.01–1.12	0.0128*
BP −140/−90 mm Hg	1.00			1.00		
BP 140–150/90–95 mm Hg	1.13	1.04–1.23	0.0035*	1.08	1.04–1.14	0.0007*
BP 150–160/95–100 mm Hg	1.17	1.05–1.29	0.0034*	1.19	1.12–1.26	<0.0001*
BP 160+/100+ mm Hg	1.33	1.19–1.48	<0.0001*	1.26	1.17–1.35	<0.0001*
Treated hypertention	1.39	1.30–1.50	<0.0001*	1.20	1.16–1.25	<0.0001*
IGT (−)	1.00			1.00		
IGT (+)	0.86	0.79–0.93	0.0002*	0.80	0.76–0.85	<0.0001*
Diabetes (−)	1.00			1.00		
Diabetes (+)	0.71	0.61–0.84	<0.0001*	0.76	0.68–0.86	<0.0001*
Treated diabetes	1.20	1.05–1.38	<0.0001*	1.12	1.01–1.24	<0.0001*
Hypercholesterolemia (−)	1.00			1.00		
Hypercholesterolemia (+)	1.01	0.94–1.08	0.8865	0.95	0.92–0.98	0.0026*
Low HDL-C (−)	1.00			1.00		
Low HDL-C (+)	1.10	1.03–1.19	0.0084*	1.02	0.97–1.08	0.4101
Hypertriglyceridemia (−)	1.00			1.00		
Hypertriglyceridemia (+)	1.04	0.98–1.11	0.2121	1.10	1.07–1.14	<0.0001*
Obesity (−)	1.00			1.00		
Obesity (+)	1.03	0.96–1.10	0.3979	1.06	1.03–1.10	0.0006*
Never smoking	1.00			1.00		
Previous smoking	1.05	0.97–1.13	0.2232	1.10	0.88–1.37	0.4007
Current smoking	1.13	1.05–1.22	0.0007*	1.16	1.06–1.26	0.0009*
Never drinker	1.00			1.00		
Occasional drinker	0.96	0.88–1.05	0.3721	0.89	0.83–0.97	0.0052*
Ethanol < 20 g/day	0.92	0.86–0.98	0.0065*	0.91	0.83–1.00	0.0414*
Ethanol > 20 g/day	0.93	0.79–1.10	0.4214	0.59	0.22–1.56	0.2846

BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IGT, impaired glucose tolerance.
*P < 0.05.

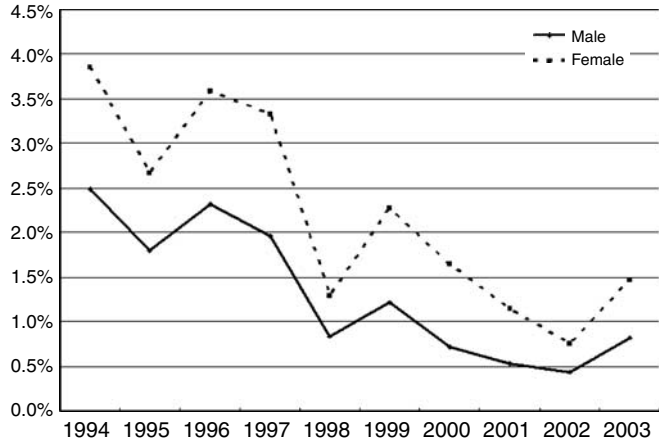

Figure 5 | Trend of annual incidence rate of CKD stage III or higher by sex. In the early years of follow-up, a higher incidence of developing CKD stage III or higher was also observed. However, after 1998, the yearly incidence of CKD stage III or higher was about 0.8% for male subjects and about 1.5% for female subjects.

Table 4 | Prevalence of newly developed CKD among the subjects

	Age (years)					
	40–49	50–59	60–69	70–	Total	%
Male						
Stage I	64	94	147	22	327	0.82
Stage II	147	276	867	431	1721	4.30
Stage III–	105	540	2343	1467	4257	10.38
Female						
Stage I	93	141	52	9	295	0.36
Stage II	213	490	876	385	1964	2.41
Stage III–	742	3531	8063	3065	15 154	18.31

CKD, chronic kidney disease.

Prevalence of CKD among the cohorts

During the 10-year follow-up period, we found that 327 subjects had CKD stage I, 1721 subjects had CKD stage II, and 4455 subjects had CKD stage III or higher, of whom 198 subjects already had proteinuria at the baseline (Table 4). Consequently, 4257 male subjects newly developed CKD stage III or higher. We found that 295 female subjects had CKD stage I, 1964 had CKD stage II, and 15 401 had CKD stage III or higher, of whom 247 already had proteinuria at the baseline. Consequently, 15 154 female subjects newly developed CKD stage III or higher. Overall, the prevalence of newly developed CKD over the 10 years was 23 718 subjects (19.2%) over 40 years of age.

DISCUSSION

The subjects in the present study were a large group of community-based individuals who underwent annual health examinations under the auspices of the local governments and the Ministry of Health, Labor and Welfare of Japan. Our study demonstrated that 23 718 subjects (19.2%) had developed CKD during the 10-year follow-up period. Predicting factors for the development of CKD showed a slight difference between CKD stage I and II (proteinuria), and CKD stage III or higher, as well as between genders. Age, blood pressure levels, and smoking habits had the same effect on all of CKD stages. However, diabetes, obesity, hyperlipidemia, and alcohol consumption had different effects on the incidence of each CKD stage.

The prevalence of proteinuria and renal failure were influenced by age and gender.[13,14] Age is recognized as an independent risk factor for renal disease[15] and our findings of increased incidence of proteinuria with aging are consistent with previous reports.[13,16–18] Also, an increased incidence of renal dysfunction with aging is consistent with previous reports. In subjects older than 50 years, the percentage of sclerotic glomeruli increased, with a range of 0.5–36%,[19] due to glomerular ischemia secondary to the changes in renal blood flow that occur with aging.[20,21] These changes resulted in not only progressive renal dysfunction but also proteinuria due to glomerular hypertension and hyperfiltration of residual glomeruli.

Proteinuria and hypertension are recognized as strong predictors for progression of renal dysfunction.[22] Klag *et al.* reported a strong, graded relationship between blood pressure and ESRD in men.[23] We found a graded relationship between blood pressure and newly onset CKD in both genders. Furthermore, the subjects with treated hypertension had a higher risk for developing CKD than other hypertensive subjects: these subjects may have had a long-standing history of hypertension resulting in vascular damage. Recent studies have suggested that strict blood pressure control and certain classes of antihypertensive medications, such as angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, reduce proteinuria and prevent progression to ESRD.[22] In this study, we had no information about any antihypertensive drugs which the treated hypertensive subjects might have been taking. Further prospective studies are needed to clarify the effectiveness of strict blood pressure control, or certain classes of antihypertensive medication such as angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, on the development of CKD.

Diabetes is also considered to be a predictor for developing proteinuria[13,18] and progression to renal dysfunction.[24,25] Our findings of an increased incidence of proteinuria with diabetes are consistent with previous reports. However, a reduced risk for developing CKD stage III in IGT or diabetes was observed. In general, patients with diabetes exhibited small amount of albumin in their urine in 20–40% of patients with type I or type II diabetes after 10–15 years of stable renal function or even hyperfiltration.[26] Consequently, some subjects with IGT or diabetes showed hyperfiltration, and these subjects maintained their renal function within the normal range, whereas patients treated for diabetes, who had

long-standing diabetic status, often progressed to CKD stage III or higher during the follow-up period.

Hyperlipidemia is also considered to be a risk factor for developing CKD.[25,27] Although hypertriglyceridemia is regarded as an independent risk factor for developing proteinuria,[28,29] the effect of total cholesterol and HDL-C on proteinuria development is controversial.[18] Metcalf *et al.* reported that the degree of albuminuria showed piecewise log-linear relationships with hypertriglyceridemia and hypercholesterolemia, and a negative piecewise linear relationship with HDL-C.[17] On the contrary, Tozawa *et al.* reported that hypertriglyceridemia was a significant predictor of proteinuria, but hypercholesterolemia and low HDL-C were not within three years follow-up period.[28] The effect of hyperlipidemia on progression of renal dysfunction produced more complex results. Schaeffner *et al.* reported that the relative risk for elevated creatinine was 1.77 for hypercholesterolemia, and 2.16 for low HDL-C in male subjects.[27] However, Munter *et al.* reported that the relative risk for elevated creatinine was 1.65 for hypertriglyceridemia and 2.13 for low HDL-C, but that hypercholesterolemia was not a significant risk factor.[25] Several other community-based studies showed that total cholesterol was not a significant risk factor for developing renal dysfunction.[30] From our results, long-term hypercholesterolemia, hypertriglyceridemia, and low HDL-C were risk factors for developing proteinuria in both genders, whereas low HDL-C in male subjects and hypertriglyceridemia in female subjects were independent relative risk factors for developing renal dysfunction. Furthermore, female subjects with hypercholesterolemia showed a reduced risk of developing renal dysfunction. Although cholesterol-lowering treatment showed favorable effects on renal function,[31,32] there are no large studies proving the effect of lipid reduction on the progression of renal disease. Our study confirmed that hyperlipidemia and low HDL-C were independent risk factors for proteinuria, and as mentioned above, proteinuria is regarded as a strong predictor for renal dysfunction. However, these lipidemic changes did not persistently affect renal function during the 10-year follow-up. Further long-term studies are needed to clarify this point.

Obesity is a known risk factor for proteinuria.[13] The renal effects of obesity include an increased glomerular filtration rate, increased renal blood flow, and renal hypertrophy,[33] and weight loss of obese subjects ameliorates these abnormalities, as well as reducing urinary protein excretion.[33] Our findings are consistent with other reports that obese subjects showed a 42% increased risk of developing proteinuria for male subjects, and a 56% increase for female subjects. However, the effect of obesity on developing CKD III or a later stage remains controversial. Iseki *et al.*[34] reported that obesity was not a major risk factor for development of ESRD in a 10-year follow-up period. Recently, Fox *et al.*[30] and Iseki *et al.*[35] reported that obesity was an independent risk factor for development for renal dysfunction following 17–18.5 years follow-up. Our cohorts showed a 6% increased risk of developing renal dysfunction only in female subjects over a 10-year follow-up period. Consequently, it is possible that obesity might be a significant relative risk for renal dysfunction after a longer follow-up duration in both genders.

Smoking is an independent risk factor for the development of CKD.[36] Our cohort also showed that smoking induced increased the risk of proteinuria and renal dysfunction in both genders. However, being an ex-smoker was not a risk factor for developing proteinuria and renal dysfunction. Consequently, cessation of smoking has a favorable effect on preventing the development of CKD.

Several population-based studies have suggested that moderate alcohol intake has a protective effect on cardiovascular death.[37,38] The effects of alcohol consumption on development of CKD remain controversial. Knight *et al.* reported that moderate alcohol intake had no substantial adverse effect on renal function in women,[39] whereas Perneger *et al.* reported significantly increased odds of developing ESRD in subjects who drank more than two alcoholic beverages per day.[40] As for developing CKD, our cohorts showed that alcohol intake of less than 20 g/day reduced the risk of developing proteinuria in men and reduced the risk of developing renal dysfunction in both genders. This favorable effect was diminished after ethanol intake of more than 20 g/day. We did not study the type of alcoholic beverage among our cohorts, although there is a possibility that the type of alcohol may influence the effects.[38] However, it is valuable to know that regular moderate alcohol consumption protects against developing CKD, but this effect is diminished after consuming more than 20 g/day of ethanol among general population.

The prevalence of CKD among our study population at the baseline in 1993 was 8.5% for male and 9.1% for female subjects. Subsequently, 19.2% of the cohort developed CKD over the next 10 years. A previous report suggested that the prevalence of CKD was 16% of a study population among individuals aged 45 years and older.[41] There may have been selection bias in our study population, because our subjects received annual physical checks for 10 years, and subjects with severe disorders, or signs or symptoms tend to attend clinics and hospitals, and thus these subjects did not receive annual physical checks. Consequently, the prevalence of CKD might have increased if we had observed these subjects.

From our study, several lifestyle-related and co-morbid conditions affected the development of CKD. The effect of active health-care education and intervention in our cohort to prevent CKD development should be studied in the near future.

In summary, the prevalence of newly developed CKD over 10 years was 23 718 (19.2%) in adults over 40 years of age. The subjects of the present study were a large group of community-based individuals who underwent annual health examinations under the auspices of the local governments and the Ministry of Health, Labor and Welfare of Japan. We found several significant risk factors for developing CKD.

Blood pressure levels, diabetes status, serum lipid status, obesity, smoking, and alcohol consumption affected the development of CKD. Further studies are needed to clarify the effects of controlling these risk factors on the prevention of CKD.

MATERIALS AND METHODS

Subjects

All the subjects in this study were participants in the annual health examination held in Ibaraki prefecture, Japan, between 1993 and 2003. At the initial screening, a total of 191 006 adults (male: 65 368, female: 125 698) aged 40 years or over underwent an annual health examination at the Ibaraki health-care center in 1993. The study protocol was approved by the Ethics Committee of Ibaraki Prefectural Office. CKD and its stages were defined from estimated GFR of <60 ml/min/1.73 m^2 or dipstick proteinuria ($\geqslant 1+$) as follows: Stage 1 CKD was defined as an estimated (e)GFR $\geqslant 90$ ml/min/1.73 m^2 and proteinuria. Stage 2 CKD was eGFR 60–89 ml/min/1.73 m^2 and proteinuria. Stages 3–5 CKD were classified to the level of kidney function (eGFR 30–59, 15–29, and <15 ml/min/1.73 m^2, respectively), regardless of the presence of other markers of kidney damage.[5]

The number of patients with CKD and the classifications of all participants at the initial screening in 1993 are shown in Table 5. In total, 5521 male subjects of 65 368 subjects (8.4%) had CKD and 11 454 female subjects of 125 698 (9.1%) had CKD. For the follow-up study, we excluded subjects who already had CKD stage III and over, and 67 302 (male: 24 356, female: 42 936) who did not receive annual examinations continuously. For the follow-up study on developing proteinuria, 1806 (male: 886, female: 920) were excluded because they had proteinuria (CKD I or II) at the initial screening in 1993.

All subjects were interviewed to obtain information regarding alcohol intake, smoking habits, and medical history, including use of antihypertensive and diabetes medications. Blood pressure was measured after several minutes' rest in a sitting position with a mercury sphygmomanometer or automatic device. The blood pressure measurement was repeated if the first reading was outside the normal range.

Proteinuria and hematuria were tested using dipsticks (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). The median for serum creatinine was 1.0 mg/dl for male subjects and 0.8 mg/dl for female subjects over the 10 years of the study.

GFR was estimated from adjusted serum creatinine using the simplified equation developed from the MDRD Study[7] as follows:

$$\text{GFR (ml/min/1.73 m}^2) = 186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for female subjects}).$$

The serum creatinine value used for the MDRD equation was measured at the Cleveland Clinic Laboratory as the measurement of serum creatinine can vary across different laboratories. Serum creatinine was calibrated as previously described.[30] First, the National Health and Nutrition Examination Survey III creatinine value was calibrated to the Cleveland Clinic Laboratory, requiring a correction factor of 0.23 mg/dl. Then, mean creatinine values from our study, by gender-specific age groups, were aligned with the corresponding corrected National Health and Nutrition Examination Survey III age-specific and sex-specific means. Overall mean differences between National Health and Nutrition Examination Survey III and our cohort were 0.17 mg/dl. Consequently, we reduced 0.06 from each creatinine value before calculating GFR.

Measurements of blood glucose, total cholesterol, triglycerides, and HDL-C were measured using an autoanalyzer (Hitachi 7350, Hitachi Ltd, Tokyo, Japan or RX-20, JEOL Ltd, Tokyo, Japan).

Hypertension was defined according to World Health Organization blood pressure criteria and the use of antihypertensive medications in 1993 as follows: subjects taking antihypertensive medication at the baseline were defined as hypertension-treated (treated hypertension); subjects having systolic blood pressure $\geqslant 140$ mm Hg and diastolic blood pressure $\geqslant 90$ mm Hg were defined as hypertensive. Diabetes was defined as follows: subjects who were receiving oral hypoglycemic or insulin treatment were defined as treated diabetes; subjects with fasting blood sugar $\geqslant$ 126 mg/dl or random blood sugar $\geqslant 200$ mg/dl were defined as diabetic; subjects with fasting blood sugar levels between 110 and 126 mg/dl or random blood sugar level between 140 and 200 mg/dl were defined as IGT. Hypercholesterolemia was defined as total cholesterol $\geqslant 220$ mg/dl, low HDL-C was defined as HDL-C $\leqslant 35$ mg/dl, and hypertriglyceridemia was defined as triglycerides $\geqslant 250$ mg/dl.

Alcohol intake was defined as follows: total alcohol consumption in grams per day was calculated from questions on the number of glasses of wine, beer, fortified wines, sake, and liqueurs/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, less than 20 g/day, and more than 20 g/day.

Smoking habits were classified into three categories: non-smoker, previous smoker, or current smoker. Obesity was defined as a body mass index $\geqslant 25$ kg/m^2, calculated as body weight in kilograms divided by the square of the height in meters.

Table 5 | Classification of CKD among 191 066 adults at initial screening held in 1993

	Male				Female			
Stage	*n*	%	Mean age (years)	Age range (years)	*n*	%	Mean age (years)	Age range (years)
I	365	0.6	58	40–86	338	0.3	52	40–79
II	1340	2.0	65	40–94	1519	1.2	63	40–89
III	3724	5.7	71	40–98	9487	7.5	70	40–96
IV	65	0.1	73	53–91	95	0.1	70	41–91
V	27	0.0	68	45–88	15	0.0	65	42–83
Total	5521	8.4			11 454	9.1		

CKD, chronic kidney disease.

Statistical methods

The primary outcome for the analysis was an estimate of GFR <60 ml/min/1.73 $m^{2.}$ (CKD stage III or higher) and the development of proteinuria (CKD stage I or II) during the follow-up period. Variables were age, proteinuria (categorized as (−, +, and + +), or more), hematuria (categorized as (−, +, and + +), or more), concomitant proteinuria and hematuria (−, +), IGT (−, +), diabetes (−, +, and treated diabetes), hypertension (categorized as systolic blood pressure −140 mm Hg and/or diastolic blood pressure −90 mm Hg, systolic blood pressure 140–150 mm Hg and/or diastolic blood pressure 90–95 mm Hg, systolic blood pressure 150–160 mm Hg and/or diastolic blood pressure 95–100 mm Hg, systolic blood pressure 160 mm Hg and/or diastolic blood pressure 100 mm Hg and treated hypertension), hypercholesterolemia (−, +), low HDL-C (−, +), hypertriglyceridemia (−, +), obesity (−, +), cigarette smoking (never, previous smoker, and current smoker), alcohol consumption (never, occasional drinker, alcohol consumption <20 g/day, and alcohol consumption $\geqslant 20$ g/day). In the follow-up study of proteinuria, GFR was included as a variable, but proteinuria, and concomitant proteinuria and hematuria were excluded from the variables. HRs of renal failure development or 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). If a variable was categorical, the first category in the parenthesis in the previous definition was defined as the baseline in the Cox model. A *P*-value of less than 0.05 was considered statistically significant.

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