ischemic heart disease [5, 6] and stroke [6–8]. Heavy drinkers are at a higher risk of these diseases whereas mild to moderate alcohol consumption, which generally corresponds to 1–2 drinks (15–30 g of alcohol) per day or less, is associated with a lower incidence of these diseases and even all-cause mortality [9]. Interestingly, a conventional marker of excessive alcohol consumption, serum γ-glutamyltransferase (GGT) level [10], has recently attracted a great deal of attention as a marker of oxidative stress [11] and a significant predictor of hypertension [12], diabetes [13], ischemic heart disease [14, 15] and stroke [15]. Based on these evidences, a clinically relevant question is whether alcohol consumption or GGT is a more practical predictor of the atherosclerotic disease. Several studies reported that higher serum GGT level was associated with the incidence of diabetes regardless of alcohol consumption [16, 17], suggesting that GGT is potentially a more useful marker to identify subjects at higher risk of diabetes, compared with alcohol consumption.

Chronic kidney disease (CKD) characterized by reduced glomerular filtration rate (GFR) and proteinuria is currently regarded as one of the critical predictors of cardiovascular disease [18]. Similar to cardiovascular disease, modifiable lifestyles such as smoking [19, 20], sleep [21] and exercise [22] contribute to CKD [23]. However, the effect of alcohol consumption on CKD remains unknown. Recent cohort studies have shown that moderate alcohol consumption attenuates the decline of GFR [24]. In contrast, whether heavy alcohol consumption affects renal prognosis [25, 26] or not [27–29] remains controversial. Regarding GGT, higher serum GGT level is associated with the CKD incidence [30, 31], identifying GGT as a predictor of CKD independent of alcohol consumption. However, these studies did not compare the clinical impact of GGT and alcohol consumption on CKD.

The aim of the present study is to compare the association between alcohol consumption and serum GGT level with proteinuria in a nationwide cross-sectional survey of the annual health checkup system in Japan. The results of the present study indicate that serum GGT level is a clinically relevant marker of CKD in both drinkers and non-drinkers.

Materials and methods

Study population

The present nationwide cross-sectional survey is described in details elsewhere [32–38]. Briefly, the present study included members of the general Japanese population who underwent the annual specific health checkups between April 2008 and March 2009, which The Ministry of Health, Labor and Welfare of Japan developed as a national health promotion system for the insured population aged 40 years or older. We analyzed the data of the participants in the health checkups in 8 prefectures (Miyagi, Fukushima, Ibaraki, Tokyo, Niigata, Osaka, Fukuoka and Okinawa prefectures). Of the 506,290 participants aged 40 years or older (Miyagi 16,640, Fukushima 50,304, Ibaraki 39,775, Tokyo 40,278, Niigata 58,882, Osaka 25,097, Fukuoka 149,785 and Okinawa 125,529), 332,296 participants (65.6 %) were included in the present analysis; 4,800 (0.9 %) participant with history of chronic renal failure and 169,194 (34.4 %) participants with missing data were excluded. The study protocol was approved by the ethics committee in Fukushima Medical University (No. 715) and Osaka University Hospital (No. 13085).

Measurements

Demographic, physical, and laboratory data included age, sex, body mass index [BMI; weight (kg)/height^2 (m^2)], mean arterial pressure [MAP; diastolic blood pressure + (systolic blood pressure−diastolic blood pressure)/3], and hemoglobin A1c, serum creatinine, triglyceride, low-density lipoprotein cholesterol, aspartate aminotransferase, alanine aminotransferase, and GGT levels. The estimated glomerular filtration rate (eGFR) was calculated using the equation, eGFR (mL/min/1.73 m^2) = 194 × age (years)$^{-0.287}$ × serum creatinine (mg/dL)$^{-1.094}$ (×0.739, if female) [39]. Proteinuria was defined primarily as ≥1+ of urinary protein by dipstick test and secondarily as ≥2+.

Information regarding lifestyle factors, current medication for comorbidities, and past history was based on the self-reported standard questionnaires that all participants were required to fill out at the time of their checkup. Alcohol consumption was ascertained by asking the following 2 questions: "How often do you drink alcoholic beverages? (1) Every day, (2) occasionally, or (3) rarely"; and "How many alcoholic beverages do you drink on the days you do drink? [About 500 mL beer, 80 mL "shochu" (a Japanese liquor similar to vodka), 60 mL whiskey, or 240 mL wine is assumed to constitute 1 standard drink.] (1) ≤1 drink per day, (2) 1–2 drinks per day, (3) 2–3 drinks per day, or (4) ≥3 drinks per day". The ethanol content per drink was calculated to be equivalent to 20 g. We regarded (3) 2–3 drinks per day and (4) ≥3 drinks per day as heavy drinking and then categorized alcohol consumption as follows: (1) rare, (2) occasional, (3) mild (ethanol intake ≤19 g/day), (4) moderate (20–39 g/day), or (5) heavy (≥40 g/day). Smoking status was evaluated from positive answers to the question "Do you smoke?" Current treatments for hypertension, dyslipidemia, and diabetes were assessed based on positive answers to the question "Are you being treated for hypertension, dyslipidemia, and

diabetes?" History of CVD, defined as a combination of cardiac disease and/or stroke, was determined by positive answers to the questions "Have you been diagnosed with CVD?"

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), and categorical variables were expressed as number (percentage). Dose (exposure-level)-response association of alcohol consumption and GGT quartiles with other clinical characteristics were tested using the Cochran–Armitage test for trend and the non-parametric test for trend across ordered groups [40].

To clarify the associations of alcohol consumption and GGT with proteinuria, their prevalence rate ratios (PRRs) were calculated using Poisson regression models with robust variance [41] after adjusting for area and clinically relevant factors. Triglyceride levels were logarithmically transformed because of their skewed distribution. Goodness-of-fit was assessed using the deviance statistic. Linearity of associations with proteinuria was assessed by significance of quadratic terms. We calculated P for trend across the median GGT value of GGT quartiles. To compare the impact on proteinuria between alcohol consumption and GGT, all subjects were categorized into 5 × 4 categories based on alcohol consumption categories and GGT quartiles [30, 31] and their prevalence rate ratios were calculated using rare drinkers in the lowest GGT quartile as a reference. To identify the optimal cutoff point of GGT, we calculated the Youden index of GGT where the sum of sensitivity and specificity is maximized [42].

All P values were based on 2-sided tests of significance. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Stata version 11.0 (Stata corp., College Station, TX, USA) and R version 2.13.1 (The R Foundation for Statistical Computing, http://www.r-project.org/).

Results

The clinical characteristics of 134,600 men and 197,696 women stratified by alcohol consumption categories are listed in Tables 1 and 2, respectively. Statistically significant trends were observed in all measurements. Heavier drinkers were younger and had a higher eGFR, higher prevalence of current smokers, and lower prevalence of dyslipidemia, diabetes, and past history of CVD. Their clinical characteristics stratified on GGT quartiles were listed in Supplementary Tables 1 and 2. Statistically significant trends were observed in all measurements except current treatment for diabetes and past history of CVD in men. Higher serum GGT level was associated with higher body mass index, higher mean arterial pressure, higher prevalence of current smokers and drinkers in both men and women.

Prevalence of proteinuria defined as ≥1+ and ≥2+ of urinary protein was 7.5 % ($N = 10{,}105$) and 2.5 % ($N = 3{,}387$) in men, respectively, and 3.7 % ($N = 7{,}229$) and 0.9 % ($N = 1{,}836$) in women, respectively. A U-shaped association between alcohol consumption and proteinuria was observed in both men and women (Fig. 1a, b). Prevalence of proteinuria was lowest in mild drinkers (1+ and ≥2+ of urinary protein: 4.2 and 2.3 % in men and 2.0 and 0.6 % in women, respectively), whereas highest in heavy drinkers (5.6 and 2.5 % in men and 3.3 and 1.2 % in women, respectively). An association between GGT and proteinuria was in a stepwise fashion in both men and women (Fig. 1c, d). Prevalence of proteinuria was lowest in the lowest GGT quartile group (3.9 and 1.8 % in men and 2.1 and 0.6 % in women, respectively) and highest in the highest GGT quartile group (6.5 and 3.5 % in men and 3.7 and 1.4 % in women).

To assess associations between alcohol consumption and proteinuria defined as ≥1+ of urinary protein, PRRs of each category of alcohol consumption were calculated in area-adjusted and multivariate-adjusted models. After adjusting clinically relevant factors, a J-shaped, rather than a U-shaped, association between alcohol consumption and proteinuria was observed in men (Fig. 2a). Statistically significant quadratic terms of alcohol consumption indicated a non-linear association. PRR was lowest in mild drinkers [vs. rare drinkers; area-adjusted PRR, 0.83 (95 % confidence interval 0.78–0.89); multivariate-adjusted PRR, 0.85 (0.80–0.91)] and highest in heavy drinkers [area-adjusted PRR, 1.05 (0.98–1.12); multivariate-adjusted PRR, 1.29 (1.05–1.59)]. A similar J-shaped association was observed in women [area-adjusted and multivariate-adjusted PRR of mild drinkers, 0.69 (0.61–0.79) and 0.79 (0.69–0.90), respectively; area-adjusted and multivariate-adjusted PRR of heavy drinkers, 1.13 (0.92–1.39) and 1.29 (1.05–1.59), respectively] (Fig. 2b). On the contrary, an association between GGT and proteinuria was linear in both men and women (Fig. 2c, d). Compared with the lowest GGT quartile as a reference (GGT ≤22 IU/L in men and ≤15 IU/L in women), area-adjusted and multivariate-adjusted PRRs of the highest quartile (≥55 IU/L in men and ≥29 IU/L in women) were 1.78 (1.69–1.88) and 1.41 (1.34–1.50) in men, respectively, and 1.87 (1.75–1.99) and 1.32 (1.24–1.41) in women, respectively.

To compare the impact of GGT and alcohol consumption on proteinuria, 134,600 men and 197,696 women were classified into 20 categories [4 (GGT quartiles) × 5 (categories for alcohol consumption)], and their PRRs were

Table 1 Clinical characteristics of 134,600 men stratified by alcohol consumption

	Alcohol consumption					*P* trend
	Rare	Occasional	Mild (≤19 g/day)	Moderate (20–39 g/day)	Heavy (≥40 g/day)	
N	40663	33924	16270	28655	15088	
Age (year)	67 (60, 71)	66 (58, 70)	68 (63, 71)	67 (61, 70)	64 (56, 68)	<0.001
BMI (kg/m^2)	23.8 ± 3.2	23.9 ± 3.1	23.3 ± 2.8	23.5 ± 2.8	23.6 ± 3.0	<0.001
MAP (mmHg)	94 ± 12	95 ± 11	96 ± 11	97 ± 11	99 ± 12	<0.001
Current smokers [*n* (%)]	9315 (22.9)	7252 (21.4)	3528 (21.7)	8406 (29.3)	6048 (40.1)	<0.001
Current treatment for						
Hypertension [*n* (%)]	11728 (28.8)	10690 (31.5)	5568 (34.2)	10844 (37.8)	5352 (35.5)	<0.001
Dyslipidemia [*n* (%)]	5186 (12.8)	4026 (11.9)	1885 (11.6)	2928 (10.2)	1240 (8.2)	<0.001
Diabetes [*n* (%)]	3476 (8.6)	2645 (7.8)	1101 (6.8)	1740 (6.1)	785 (5.2)	<0.001
Past history of CVD [*n* (%)]	5839 (14.4)	4069 (12.0)	2128 (13.1)	3274 (11.4)	1374 (9.1)	<0.001
Triglyceride (mg/dl)	112 (81, 160)	112 (79, 162)	105 (76, 150)	110 (77, 161)	120 (82, 186)	<0.001
LDL cholesterol (mg/dL)	125 ± 30	122 ± 29	120 ± 28	116 ± 29	111 ± 31	<0.001
Hemoglobin A1c (%)	5.5 ± 0.9	5.4 ± 0.8	5.4 ± 0.7	5.3 ± 0.7	5.3 ± 0.8	<0.001
GGT (IU/L)	25 (19, 37)	31 (22, 48)	33 (23, 50)	43 (28, 71)	60 (37, 111)	<0.001
AST (IU/L)	22 (18, 26)	22 (19, 27)	23 (19, 27)	24 (20, 29)	26 (22, 33)	<0.001
ALT (IU/L)	21 (16, 28)	21 (16, 28)	19 (15, 26)	20 (16, 27)	22 (17, 31)	<0.001
eGFR (ml/min/1.73 m^2)	72 ± 16	74 ± 16	73 ± 15	76 ± 16	79 ± 16	<0.001
Urinary protein [*n* (%)]						
Negative or trace	37457 (92.1)	31353 (92.4)	15224 (93.6)	26590 (92.8)	13871 (91.9)	0.066*
1+	2073 (5.1)	1696 (5.0)	679 (4.2)	1434 (5.0)	836 (5.6)	<0.001†
2+ or more	1133 (2.8)	875 (2.6)	367 (2.3)	631 (2.2)	381 (2.5)	

Mean ± SD, median (25, 75 %)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *GGT* γ-glutamyltransferase, *LDL* low-density lipoprotein, *MAP* mean arterial pressure

* Negative or trace vs. 1+ or more

† 1+ or less vs. 2+ or more

Table 2 Clinical characteristics of 197,696 women stratified by alcohol consumption

	Alcohol consumption					*P* trend
	Rare	Occasional	Mild (≤19 g/day)	Moderate (20–39 g/day)	Heavy (≥40 g/day)	
N	141840	40270	8865	4748	1973	
Age (year)	66 (61, 70)	65 (58, 69)	64 (59, 69)	60 (53, 66)	56 (47, 62)	<0.001
BMI (kg/m^2)	22.9 ± 3.5	22.5 ± 3.2	21.9 ± 3.0	22.0 ± 3.1	22.0 ± 3.2	<0.001
MAP (mmHg)	92 ± 12	92 ± 12	92 ± 12	93 ± 12	93 ± 13	0.310
Current smokers [*n* (%)]	5761 (4.1)	2731 (6.8)	869 (9.8)	1159 (24.4)	776 (39.3)	<0.001
Current treatment for						
Hypertension [*n* (%)]	40813 (28.8)	9919 (24.6)	2146 (24.2)	1177 (24.8)	442 (22.4)	<0.001
Dyslipidemia [*n* (%)]	30667 (21.6)	7170 (17.8)	1322 (14.9)	547 (11.5)	142 (7.2)	<0.001
Diabetes [*n* (%)]	6265 (4.4)	1024 (2.5)	172 (1.9)	87 (1.8)	28 (1.4)	<0.001
Past history of CVD [*n* (%)]	11372 (8.0)	2641 (6.6)	560 (6.3)	281 (5.9)	104 (5.3)	<0.001
Triglyceride (mg/dl)	98 (72, 136)	92 (67, 128)	86 (64, 118)	88 (64, 125)	100 (68, 148)	<0.001
LDL cholesterol (mg/dL)	130 ± 30	129 ± 30	125 ± 29	118 ± 31	110 ± 33	<0.001
Hemoglobin A1c (%)	5.3 ± 0.6	5.3 ± 0.6	5.2 ± 0.5	5.1 ± 0.5	5.0 ± 0.5	<0.001
GGT (IU/L)	19 (15, 27)	20 (16, 29)	22 (17, 33)	27 (20, 43)	34 (22, 62)	<0.001
AST (IU/L)	22 (19, 25)	21 (19, 25)	21 (19, 25)	22 (19, 26)	22 (19, 27)	0.028
ALT (IU/L)	17 (14, 22)	17 (14, 22)	16 (13, 21)	17 (13, 22)	18 (14, 24)	<0.001
eGFR (ml/min/1.73 m^2)	75 ± 16	77 ± 16	77 ± 15	80 ± 16	84 ± 17	<0.001
Urinary protein [*n* (%)]						
Negative or trace	136388 (96.2)	38988 (96.8)	8634 (97.4)	4572 (96.3)	1885 (95.5)	<0.001*
1+	4020 (2.8)	995 (2.5)	177 (2.0)	136 (2.9)	65 (3.3)	<0.001†
2+ or more	1432 (1.0)	287 (0.7)	54 (0.6)	40 (0.8)	23 (1.2)	

Mean ± SD, median (25, 75 %)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *GGT* γ-glutamyltransferase, *LDL* low-density lipoprotein, *MAP* mean arterial pressure

* Negative or trace vs. 1+ or more

† 1+ or less vs. 2+ or more

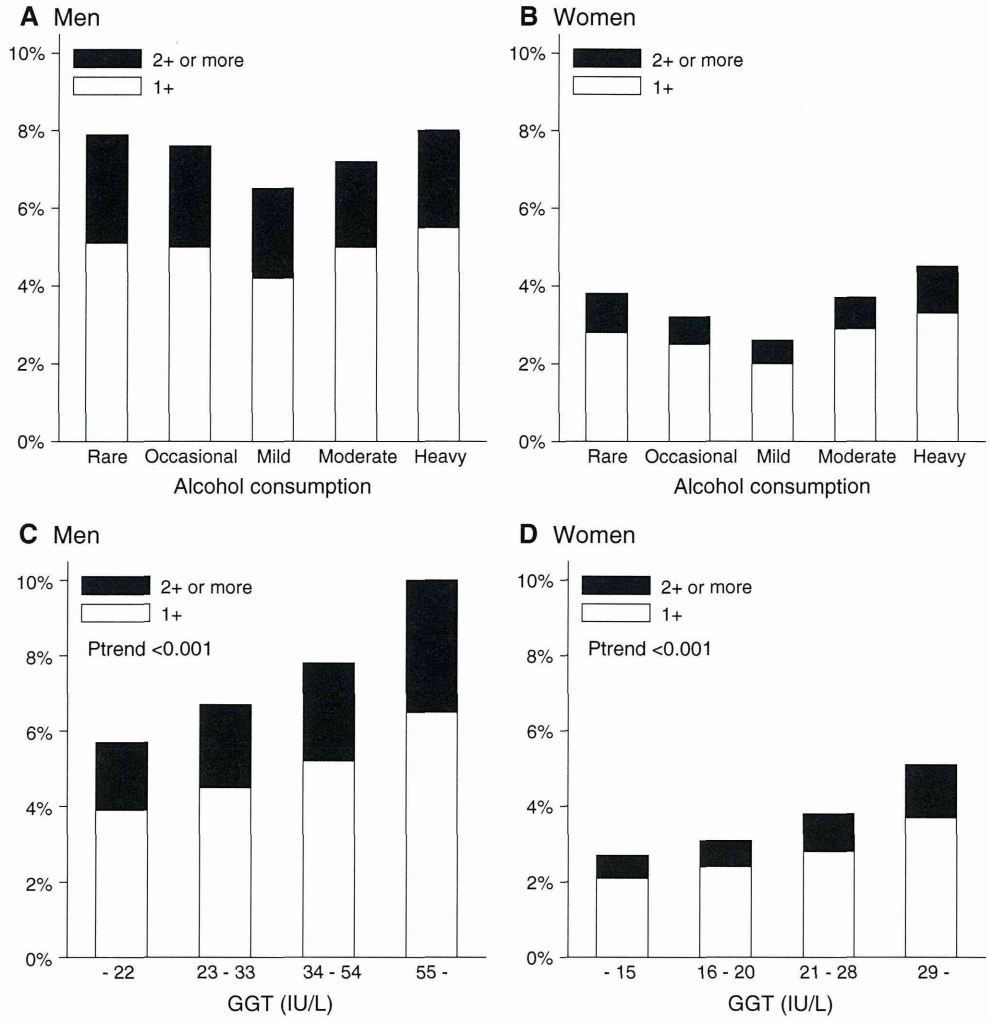

Fig. 1 Prevalence of proteinuria stratified by alcohol consumption (**a** and **b**) and serum γ-glutamyltransferase (*GGT*) quartiles (**c** and **d**) in men (**a** and **c**) and women (**b** and **d**). Alcohol consumption was categorized into rare, occasional, mild (ethanol intake ≤19 g/day), moderate (20–39 g/day), and heavy drinking (≥40 g/day)

calculated in multivariate-adjusted models. Rare drinkers with the lowest GGT quartile were set as a reference (Fig. 3). Interestingly, among men in the lowest GGT quartile (≤22 IU/L), mild to heavy drinkers had lower PRRs of proteinuria defined as ≥1+ of urinary protein, compared with rare and occasional drinkers [rare, occasional, mild, moderate and heavy drinkers in the lowest GGT quartile (≤22 IU/L): 1.00 (reference); 0.91 (0.82–1.00), 0.74 (0.63–0.86), 0.76 (0.65–0.89), 0.78 (0.57–1.06)] (Fig. 3a). Another, more interesting finding was that men in the highest GGT quartile (≥55 IU/L) had a higher PRRs, irrespective of alcohol consumption [rare, occasional, mild, moderate and heavy drinkers with highest GGT quartile (≥55 IU/L): 1.27 (1.15–1.41), 1.33 (1.21–1.46), 1.21 (1.08–1.35), 1.29 (1.18–1.40), 1.39 (1.27–1.52)]. Similar to men, women in the highest quartiles of GGT had higher PRRs (Fig. 3c). However, a stepwise association between GGT and proteinuria in each category of alcohol consumption was not as evident among the female participants as among the male participants. As a sensitivity analysis, we redefined proteinuria as ≥2+ of urinary protein and compared the impact of serum GGT level and alcohol consumption on proteinuria. Similar superiority of serum GGT level over alcohol consumption was observed (Fig. 3b, d). After excluding 20,547 (15.3 %) men and 30,991 (15.7 %) women without serum uric acid data, we also assessed the associations of serum GGT and alcohol consumption with proteinuria. The results of multivariate-adjusted models adjusting additionally for uric acid were comparable to Fig. 3, ascertaining that their associations were independent of serum uric acid (data not shown).

To identify the optimal cutoff point of GGT, we calculated the Youden index of serum GGT level. Area under the curve of receiver–operator characteristics curve was 0.571 and 0.574 in men and women, respectively. The optimal cutoff points in men and women were 43.6 IU/L

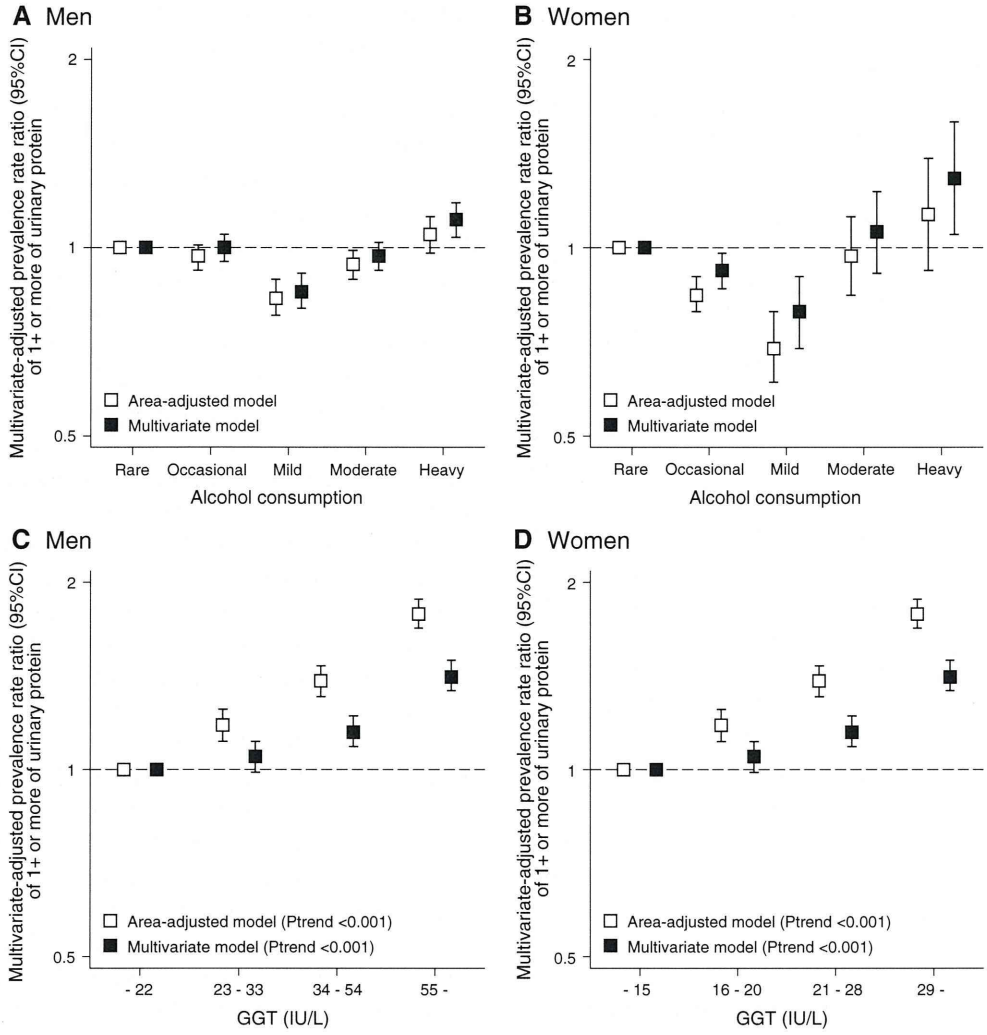

Fig. 2 Association of alcohol consumption (**a** and **b**) and serum γ-glutamyltransferase (*GGT*) level (**c** and **d**) with proteinuria defined as ≥1+ of urinary protein in men (**a** and **c**) and women (**b** and **d**). Prevalence rate ratios with 95 % confidence interval were calculated after adjusting for area in area-adjusted models and clinically relevant factors in multivariate-adjusted models, including area, age, body mass index, mean arterial pressure, current smokers, current treatment for hypertension, dyslipidemia and diabetes, past history of cardiovascular disease, log triglyceride, low-density lipoprotein cholesterol, hemoglobin A1c, and estimated glomerular filtration rate. Alcohol consumption was categorized into rare, occasional, mild (ethanol intake ≤19 g/day), moderate (20–39 g/day), and heavy drinking (≥40 g/day)

(sensitivity 0.442, specificity 0.663, positive predictive value 0.096, and negative predictive value 0.936) and 23.2 IU/L (sensitivity 0.467, specificity 0.649, positive predictive value 0.048, negative predictive value 0.970), respectively (Table 3).

Discussion

The present cross-sectional study showed that serum GGT level was associated with proteinuria independently of alcohol consumption and, more interestingly, revealed that both drinkers and non-drinkers with the higher serum GGT level had higher probability of proteinuria (Fig. 3). Based on these results, drinkers with higher serum GGT level may potentially reap the benefit of abstinence from drinking. In other words, serum GGT level possibly gives an answer to a personal question for each drinker, "to drink or not to drink?" This novel finding indicates that serum GGT level is clinically more useful to identify subjects at a higher risk of proteinuria, a predictor of ESRD [43, 44] and CVD [18], than self-reported alcohol consumption.

Although some early epidemiological studies failed to show a beneficial effect of alcohol consumption on renal prognosis [45, 46], more recent and well-designed cohort studies have showed that mild drinkers were likely to be at lower risk of a progressive GFR decline [25, 26, 29, 47–50]. However, renal prognosis of heavier drinkers is

Table 3 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of γ-glutamyltransferase (GGT) in 134,600 men and 197,696 women

	GGT (IU/L)	Sensitivity	Specificity	PPV	NPV
Men	10	0.997	0.004	0.075	0.945
	20	0.853	0.201	0.080	0.944
	30	0.636	0.461	0.087	0.940
	40	0.475	0.627	0.094	0.936
	43.6[a]	0.442	0.663	0.096	0.936
	50	0.367	0.729	0.099	0.934
	60	0.292	0.793	0.103	0.933
	70	0.237	0.838	0.106	0.931
	80	0.196	0.869	0.108	0.930
	90	0.168	0.891	0.111	0.930
	100	0.144	0.909	0.113	0.929
Women	10	0.976	0.029	0.037	0.970
	20	0.566	0.544	0.045	0.971
	23.2[a]	0.467	0.649	0.048	0.970
	30	0.305	0.789	0.052	0.968
	40	0.185	0.880	0.055	0.966
	50	0.127	0.923	0.059	0.965
	60	0.096	0.947	0.064	0.965
	70	0.072	0.962	0.066	0.965
	80	0.059	0.971	0.072	0.965
	90	0.047	0.978	0.075	0.964
	100	0.037	0.983	0.077	0.964

[a] Youden index

controversial. Some studies reported that renal prognosis of heavier drinkers was comparable with, or ever better than, that of mild drinkers [25, 26, 29, 47, 48], whereas others suggested that heavier alcohol consumption might predict a larger GFR decline [28, 47, 49]. Regarding proteinuria, only a limited number of cohort studies assessed an association between alcohol consumption and incidence of proteinuria. An Australian cohort study reported that heavier drinkers were at a higher risk of incident albuminuria in a stepwise fashion [26]. On the contrary, a Japanese cohort study revealed a U-shaped association between alcohol consumption and incidence of proteinuria [29]. Compared with the non-drinkers, the mild drinkers with <20 g/day of ethanol were at lower risk of incidence of proteinuria, whereas the heavier drinkers with ≥20 g/day of ethanol were at similar risk. Their study and ours, two Japanese large studies, led to the similar results of lowest probability of proteinuria in mild drinkers. As a previous study indicates that the renoprotective effect is different among alcohol beverages [25], different consumption patterns of alcohol beverages in different countries may affect these internationally conflicting results. Another potential reason may be the different categories of alcohol consumption. The lower limits of highest category of alcohol consumption were various; 10 [49], 15 [48], 20 [29], 30 [26], 37.5 [25], and 48 g/day [47] of ethanol intake and 1 [50] and 4 drinks/day [28] of alcohol beverages. A lower limit and, consequently, wider range of highest category of alcohol consumption may dilute an association between the highest category and proteinuria, leading to the results biased to the null. Although the present study design is cross-sectional, a larger sample size enables us to reveal a J-shape association between alcohol consumption and proteinuria after the fine and clinically relevant categorization of alcohol consumption.

Predictive value of self-reported alcohol consumption for proteinuria is easily biased due to several reasons. Self-reported alcohol consumption is notoriously vulnerable to reporting bias [51, 52]. Biased measure of alcohol consumption, consequently, blunts an association between alcohol consumption and proteinuria. Even if drinkers honestly answered their alcohol consumption, the biological differences in alcohol metabolism between individuals modify clinical effect of alcohol consumption. The alcohol metabolite acetaldehyde and acetaldehyde-induced oxidative stress are thought to be the main cause of alcohol-induced organ damage [53]. Genetic factors, such as variations in alcohol dehydrogenase, aldehyde dehydrogenase and CYP2E1, play pivotal roles in alcohol metabolism [54, 55]. Previous studies reported that polymorphisms of these genes potentially predict the incidence of CVD [56, 57] and even modify the effect of alcohol consumption on CVD [58, 59]. Accordingly, we need clinically relevant biomarkers to indicate alcohol insult more accurately than self-reported alcohol consumption. The present study suggested that GGT, a conventional marker of excessive alcohol consumption, is a potential candidate for a biomarker of a detrimental effect of alcohol consumption.

Oxidative stress, one of the key players of pathogenesis of proteinuria [60], may contribute to an association between serum GGT level and proteinuria. GGT is expressed in many kinds of cells, especially in hepatocyte and renal proximal tubular cells [61], and plays a vital role in cellular antioxidant system dependent on glutathione (GSH) [62]. Because oxidative stress induces GGT expression [63] and serum GGT level is well associated with serum marker of oxidative stress [64–66], serum GGT is now regarded as an adaptive marker of systemic oxidative stress [11]. In the present study, the drinkers with higher serum GGT level were probably exposed to higher oxidative insults and were at higher risk of proteinuria, even though their self-reported alcohol consumption was at the same level. Compatible with our hypothesis, a previous cross-sectional study reported that serum GGT is well associated with the serum makers of oxidative stress in all subgroups stratified by alcohol consumption [66].

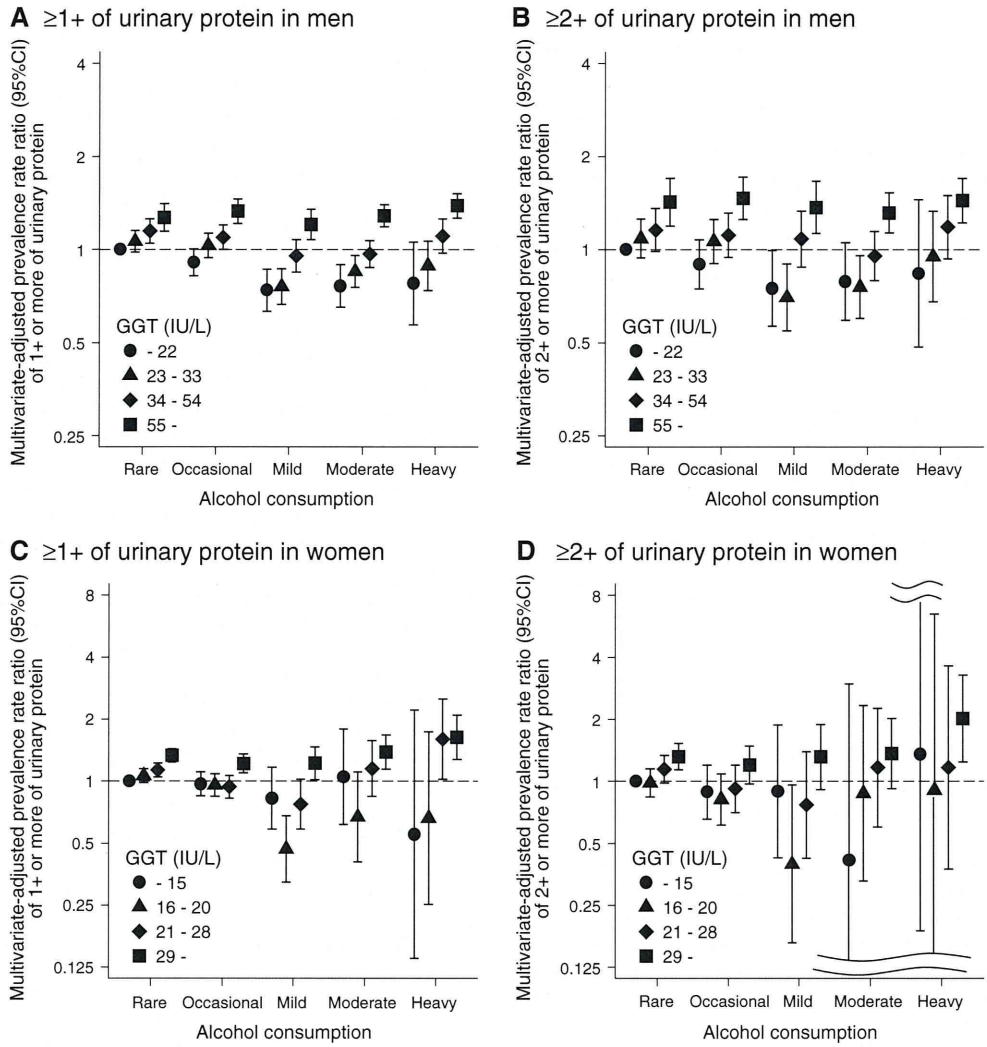

Fig. 3 Associations of GGT and alcohol consumption with proteinuria defined as ≥1+ of urinary protein by dipstick test (**a** and **c**) or ≥2+ (**b** and **d**) in men (**a** and **b**) and women (**c** and **d**) Prevalence rate ratios with 95 % confidence interval were calculated after area, age, body mass index, mean arterial pressure, current smokers, current treatment for hypertension, dyslipidemia and diabetes, past history of cardiovascular disease, log triglyceride, low-density lipoprotein cholesterol, hemoglobin A1c, and estimated glomerular filtration rate. Alcohol consumption was categorized into rare, occasional, mild (ethanol intake ≤19 g/day), moderate (20–39 g/day), and heavy drinking (≥40 g/day)

Alternatively, GGT may directly induce oxidative stress [67]. In the presence of iron or other transitional metals, cysteinylglycine, a GGT-induced GSH metabolite, potentially produces free radical species, promoting oxidative stress [68, 69]. Precise mechanisms of a link between serum GGT and proteinuria remain to be investigated.

Our study has several limitations. First, the results of the present cross-sectional study should be confirmed in a longitudinal study. Second, the impact of alcohol consumption on proteinuria in this study might be underestimated. Previous studies demonstrated that excessive alcohol consumption is a risk factor of dyslipidemia, diabetes, and cardiovascular disease. However, in this study, current treatments for dyslipidemia and diabetes and past history of cardiovascular disease were more common in the participants with lower alcohol consumption, as compared with those with higher consumption (Tables 1, 2). This paradoxical association suggests that the past health problems had affected current alcohol consumption (sick-quitter effect) [70]. Unfortunately information on the past alcohol consumption was not available in the present study, which is essential to assess a precise impact of alcohol consumption on proteinuria [71]. Third, proteinuria was determined with a single dipstick test measurement, which might lead to misclassifications. However, the majority of such misclassifications would bias our findings towards the null hypothesis and thus weaken the associations. In addition, prior studies have shown that even a single

measurement of dipstick proteinuria is a significant risk factor for all-cause mortality, cardiovascular mortality [72], and ESRD [43, 73].

In conclusion, higher serum GGT level was associated with a higher probability of proteinuria in both drinkers and non-drinkers, indicating that serum GGT level is a more useful marker to identify the subjects at higher risk of proteinuria, compared with self-reported alcohol consumption. Serum GGT level may provide a practical clue to the personalized answer to the question "to drink or not to drink?"

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Conflict of interest The authors have declared that no conflict of interest exists.

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Original Article

Annual decline in estimated glomerular filtration rate is a risk factor for cardiovascular events independent of proteinuria

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cardiovascular diseases, chronic kidney diseases, glomerular filtration rate, proteinuria, risk factor.

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SUMMARY AT A GLANCE

Previous studies have shown that annual decline or increment estimated glomerular filtration rate may influence prognosis. This study focuses on the cardiovascular events and demonstrates that the annual decline rate in eGFR is a risk factor for cardiovascular events independent of proteinuria by using a large longitudinal Japanese population-based study of participants receiving annual health checkups from 2008–2010. To reduce the incidence of cardiovascular events in the general population, serial measurement of serum creatinine to obtain the change rate in eGFR is warranted.

ABSTRACT:

Aims: **Chronic kidney disease is a risk factor of the development of cardiovascular disease (CVD). However, it is not clear whether decline of glomerular filtration rate (GFR), not reduced GFR, is a risk factor for the incidence of CVD independent of proteinuria.**

Methods: **By using a population-based 521 123 person-years longitudinal cohort receiving annual health checkups from 2008 to 2010, we examined whether the annual decline of estimated GFR is a risk factor for CVD development independent of proteinuria.**

Results: **During the follow-up period, there were 12 041 newly developed CVD events, comprising 4426 stroke events and/or 8298 cardiac events. As expected, both reduced estimated GFR and proteinuria were risk factors for the development of CVD in our study population. Moreover, annual decline of estimated GFR was a significant and independent risk factor for the incidence of CVD (HR [95% CI], 1.23 [1.18–1.28] in males or 1.14 [1.10–1.18] in females for −10% per year) with covariant adjustment for proteinuria and reduced estimated GFR.**

Conclusion: **Annual decline of GFR is an independent risk factor for CVD. Serial measurement of both creatinine and proteinuria would be better to predict the incidence of CVD in the general population.**

Chronic kidney disease (CKD) is a risk factor for not only progression to end-stage kidney disease (ESKD), but also the development of cardiovascular disease (CVD).[1–3] Reduced glomerular filtration rate (GFR) and presence of proteinuria are predictors of CVD events and all-cause mortality.[4–7] Some recent studies have focused on the relationship between annual decline of GFR and prognosis.[8–14] These studies were prompted by policies for health checkup systems that a few nations and regions including Japan have adopted that include annual screening with measurement of both serum

creatinine concentration and urinary protein. If the change in eGFR is an independent and significant risk factor for CVD or ESKD, it may make sense to follow annual eGFR measurements as part of health screening in the general population.

In the present study, by using a population-based 521 123 person-years longitudinal cohort who were participants of annual health checkups, 'The Specific health check and Guidance in Japan' between 2008 and 2010, we examined proteinuria and serum creatinine to predict the incidence of CVD, classified on the basis of the presence of proteinuria and/or reduced eGFR, and also the new CKD category based on the combination of proteinuria and eGFR levels.[15] Furthermore, we examined whether the annual change in eGFR is an independent risk factor for the incidence of CVD by using the multivariable Cox-hazard model. This analysis might provide insights for future screening policies for creatinine measurement to reduce the number of patients with CVD in the general population.

METHODS

Patients and methods

This study was conducted according to the guidelines of the Declaration of Helsinki and was granted ethical approval by the relevant institutional review boards. This was a longitudinal cohort study and was performed as part of the prospective ongoing 'Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan' project. Other details, such as the participants' area of residence, were reported previously.[16,17] Data were sent to an independent data centre, called the NPO Japan Clinical Research Support Unit, and were verified by trained staff.

The incidence of stroke or cardiac event in this study was defined as a negative history at the baseline year and a positive history in the follow-up year. Therefore, participants with a positive history for stroke, cardiac event, or both at the baseline year were excluded from this study. The subjects were observed for a 1- to 3-year follow-up period; their follow-up duration was 521 123 person-years (205 719 person-years among males and 315 404 person-years among females). The net subjects included 298 148 people (39.7% (n = 118 378) were men) from 40 to 79 years of age, for whom all of the data necessary for our research purposes were available – namely, information about age, sex, body mass index (BMI), systolic blood pressure, diastolic blood pressure, habitual smoking, use of anti-hypertensive drugs, lipid-lowering drugs, and hypoglycaemic drugs, previous history of CVD (i.e., stroke and cardiac events) obtained via a self-reported questionnaire, in addition to data concerning the serum creatinine level and dipstick urine test for proteinuria, glucose level, and lipid status.

Measurement of parameters

Urinalysis by the dipstick method was performed on a single spot urine specimen collected early in the morning after overnight fasting. Urine dipstick results were interpreted by the medical staff at each local medical institution and recorded as (−), (+/−, designated as trace), (+), (1+), (2+), and (3+) as described previously.[18] In Japan, the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) proposes that all urine dipstick results of (+) should correspond to a urinary protein level of 30 mg/dL. Proteinuria was defined as (+) or more. Blood samples were collected after an overnight fast and were assayed within 24 h with an automatic clinical chemical analyzer.

Estimated GFR was calculated from the simplified equation developed from the Modification of Diet in Renal Disease (MDRD) study[19] without adjusting for Japanese covariant factors; we separated the subjects into those with normal renal function (eGFR ≥ 60 mL/min per 1.73 m^2) and those with low renal function (eGFR < 60 mL/min per 1.73 m^2). We defined hyperglycaemia as a fasting blood sugar (FBS) of ≥126 mg/dL, and hypertension as a systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥90 mmHg.[20] Hypercholesterolemia was defined as low-density lipoprotein of ≥140 mg/dL, high-density lipoprotein cholesterol (HDL-C) of ≤40 mg/dL, or triglycerides ≥ 200 mg/dL. These co-morbid conditions at the baseline year were applied for the risk analysis.

Statistical analysis

The primary outcome for the analysis was the incidence of CVD during the follow-up period. Variables were age, diabetes, hypertension and renal function, hypercholesterolemia, low HDL-C, hypertriglyceridaemia, cigarette smoking, and annual change in eGFR. The hypertension category was defined as normotensive, untreated hypertension, treated hypertension (non-hypertensive subjects with anti-hypertensive drugs), or drug-resistant hypertension (hypertensive subjects with use of anti-hypertensive drugs). Annual change in eGFR was determined by using the baseline and the latest data. That was defined as [(Baseline eGFR − latest follow-up year eGFR)/follow-up years/eGFR at baseline year] and was analyzed with the top and bottom 5.0% removed. For analyses of annual change in eGFR, subjects without eGFR data for the follow-up years were excluded. Hazard ratios of the incidence of CVD by sex were estimated by using the Cox regression model (SAS software, version 9.3, SAS Institute, CA, USA). A P-value of <0.05 was considered statistically significant.

RESULTS

During the follow-up period, there were 12 041 CVD events (5676 among males and 6365 among females), comprising 4426 stroke events and/or 8298 cardiac events. The subjects with proteinuria or reduced eGFR exhibited older age, higher mean values of systolic and diastolic blood pressure, BMI, blood glucose, triglycerides and low-density lipoprotein, and higher prevalence of smoking, taking anti-hypertensive drugs, hypoglycaemic drugs and lipid-lowering drugs, and lower high-density lipoprotein levels than those without proteinuria or reduced eGFR (Table S1). While the incidence of CVD was 2.47% in males and 1.91% in females per person-years among the subjects with an eGFR over 60 mL/min per 1.73 m^2 and negative proteinuria at the baseline year, 3.85% in males and 2.68% in females per person-years with an eGFR lower than 60 mL/min per 1.73 m^2 and/or positive proteinuria at the baseline year (Table 1). We

Table 1 Incidence of cardiovascular disease (CVD) in the Japanese general population, categorized by reduced estimated glomerular filtration rate (eGFR) and proteinuria

	Male		Female	
UP	(–) or trace	(+) or more	(–) or trace	(+) or more
	Number of study subjects (person-years)			
eGFR (mL/min per 1.73 m^2)				
60≤	162 741	9073	270 447	7743
<60	30 228	3677	34 831	2383
	Incidence of stroke (% per person-years)			
eGFR				
60≤	0.93	1.58	0.68	1.01
<60	1.29	2.69	0.91	1.30
	Incidence of cardiac events (% per person-years)			
eGFR				
60≤	1.69	2.42	1.32	2.00
<60	2.57	3.86	1.81	2.69
	Incidence of CVD (% per person-years)			
eGFR				
60≤	2.47	3.73	1.91	2.83
<60	3.63	6.01	2.58	3.74

Population size and incidence of stroke, cardiac events, or both (CVD) are shown with categorization based on an eGFR of 60 mL/min per 1.73 m^2 and proteinuria in male and female subjects, respectively. eGFR and proteinuria at the baseline year were applied. CVD, cardiovascular diseases; eGFR, estimated glomerular filtration rate; UP, urinary protein.

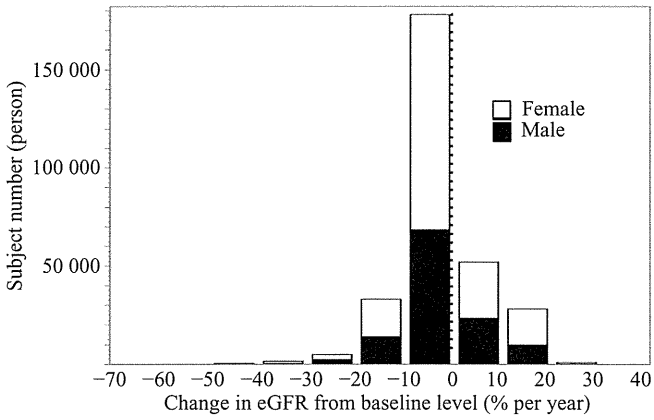

Fig. 1 Annual change in estimated glomerular filtration rate (eGFR). A histogram of the annual change in eGFR from the baseline year to the end of follow-up for each subject is shown. (□) Female; (■) male.

recalculated the incidence of CVD by using the new CKD category (Table S2). A higher incidence of stroke, cardiac event, or CVD was observed among subjects with both proteinuria and reduced eGFR with a gradual increase in incidence (Table S2). Furthermore, we examined whether CKD stage was associated with incidence of CVD after adjusting for age, sex, hypertension, diabetes, and other baseline characteristics. As expected, a higher adjusted hazard ratio for the incidence of CVD was clearly demonstrated in both male and female subjects with advanced CKD stage (Figs S1,S2). These results indicate that co-existence of reduced eGFR and proteinuria is a risk factor for the incidence of CVD in our study population.

We further investigated risk factors for the incidence of CVD by using a multivariable Cox-hazard model. Low eGFR, the presence of proteinuria, taking anti-hypertensive drugs, taking lipid-lowering drugs, taking hypoglycaemic drugs, rising BMI, and aging were all significant risk factors for the incidence of stroke, cardiac event, or CVD in both male and female subjects, with the exception of taking lipid-lowering drugs and rising BMI in males and the presence of proteinuria and rising BMI in females and for the incidence of stroke (Table 2). Interestingly, annual decline of eGFR was a significant and independent risk factor for the incidence of CVD in males and females, with covariant adjustment for proteinuria and reduced eGFR (Table 2).

We also examined the distribution of annual change in eGFR as shown in Figure 1. The median annual changes in eGFR from eGFR at the baseline year were −0.45 (10, 25, 75, or 90 percentile; +8.65, +1.34, −5.33, or −12.43, respectively) % per year among males and −0.44 (10, 25, 75, or 90 percentile; +10.34, +0.21, −4.60, or −13.85, respectively) % per year among females. We categorized the subjects into three subpopulations with an annual eGFR change from −20% to +20% per year as shown in Table 3, and subjects with a change from −10% to +10% per year were set as a reference population. The reference population showed the lowest prevalence of proteinuria and a lower incidence of CVD for both male and female subjects than almost all of the other subpopulations (Table 3). The hazard ratio for the incidence of CVD with covariant adjustment for proteinuria for each subpopulation of males or females indicated that both rapidly increasing and decreasing eGFR are significant risk factors for developing CVD (Fig. 2 and Fig. S3). The subjects with a reduced eGFR at the baseline year also had a higher risk of the incidence of CVD with rapidly increasing or decreasing eGFR than did subjects in the reference population with reduced eGFR and a change in eGFR from −10% to +10% per year (Fig. 2). The contingency of the presence of proteinuria with (2+) or more, which corresponds to a urinary protein level of ≥100 mg/dL, was examined among the subpopulations derived from annual change in eGFR. Compared to within ± 10% per year in males (1.81%) or in females (0.71%), a higher rate of proteinuria with a result of (2+) or more was observed in the subjects with an annual change in eGFR from −20% to −10% in males (2.93%) or in females (1.35%) per year ($P < 0.0001$ in males or $P < 0.0001$ in females, respectively, by the χ^2 test). In contrast, a comparable rate of proteinuria with (2+) or more was observed in the subjects with an annual change in eGFR from +10% to

Table 2 Adjusted hazard ratio for the incidence of cardiovascular disease (CVD) including annual change in eGFR

Risk factor	Male			Female		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
	Hazard ratio for the incidence of stroke					
Low eGFR (eGFR < 60 mL/min per 1.73 m^2)	1.16	1.04–1.29	<0.001	1.13	1.01–1.28	0.04
Proteinuria (+ or more)	1.47	1.27–1.70	<0.0001	1.13	0.92–1.39	0.26
Untreated HTN (SBP ≥ 140 or DBP ≥ 90 mmHg)	1.28	1.06–1.53	<0.001	1.22	0.98–1.52	0.07
Treated HTN (SBP < 140 and DBP < 90 mmHg)	1.94	1.73–2.18	<0.0001	2.01	1.80–2.24	<0.0001
HTN with treatment (SBP ≥ 140 or DBP ≥ 90 mmHg)	1.86	1.65–2.10	<0.0001	1.72	1.52–1.94	<0.0001
Hypertriglyceridaemia (TG ≥ 200 mg/dL)	0.95	0.81–1.11	0.53	1.11	0.92–1.33	0.28
High LDL (LDL ≥ 140 mg/dL)	1.09	0.97–1.22	0.16	0.99	0.87–1.11	0.81
Low HDL (HDL ≤ 40 mg/dL)	0.89	0.57–1.41	0.63	0.77	0.51–1.18	0.23
Lipid-lowering drugs (yes)	1.11	0.97–1.27	0.12	1.14	1.03–1.26	0.01
Hyperglycaemia (FBS ≥ 126 mg/dL)	0.99	0.82–1.19	0.88	1.16	0.91–1.48	0.23
Hypoglycaemic drugs (yes)	1.38	1.17–1.62	<0.0001	1.29	1.06–1.57	0.01
Smoking (current smokers)	1.06	0.95–1.18	0.32	1.14	0.93–1.41	0.19
Age (years)	1.07	1.07–1.08	<0.0001	1.08	1.07–1.09	<0.0001
BMI (+1 kg/m^2)	1.01	0.99–1.02	0.43	1.01	0.99–1.02	0.13
δGFR (–10% per year)	1.25	1.17–1.33	<0.0001	1.12	1.05–1.19	<0.001
	Hazard ratio for the incidence of cardiac events					
Low eGFR (eGFR < 60 mL/min per 1.73 m^2)	1.24	1.14–1.34	<0.0001	1.22	1.12–1.33	<0.0001
Proteinuria (+ or more)	1.27	1.13–1.43	<0.0001	1.24	1.07–1.43	<0.001
Untreated HTN (SBP ≥ 140 or DBP ≥ 90 mmHg)	0.95	0.82–1.09	0.47	1.01	0.86–1.19	0.91
Treated HTN (SBP < 140 and DBP < 90 mmHg)	1.75	1.61–1.90	<0.0001	1.80	1.67–1.95	<0.0001
HTN with treatment (SBP ≥ 140 or DBP ≥ 90 mmHg)	1.44	1.31–1.58	<0.0001	1.55	1.42–1.70	<0.0001
Hypertriglyceridaemia (TG ≥ 200 mg/dL)	1.02	0.91–1.14	0.77	1.16	1.01–1.33	0.03
High LDL (LDL ≥ 140 mg/dL)	1.04	0.96–1.14	0.34	0.91	0.83–1.00	0.04
Low HDL (HDL ≤ 40 mg/dL)	1.02	0.75–1.40	0.89	1.20	0.94–1.52	0.14
Lipid-lowering drugs (yes)	1.26	1.15–1.39	<0.0001	1.17	1.09–1.26	<0.0001
Hyperglycaemia (FBS ≥ 126 mg/dL)	1.04	0.91–1.20	0.57	1.05	0.87–1.26	0.60
Hypoglycaemic drugs (yes)	1.25	1.10–1.41	<0.001	1.27	1.10–1.47	<0.001
Smoking (current smokers)	0.97	0.90–1.06	0.49	1.16	1.01–1.34	0.04
Age (years)	1.06	1.05–1.06	<0.0001	1.06	1.06–1.07	<0.0001
BMI (+1 kg/m^2)	1.02	1.01–1.03	0.01	1.01	1.01–1.02	0.03
δGFR (–10%/year)	1.22	1.16–1.28	<0.0001	1.15	1.10–1.20	<0.0001
	Hazard ratio for the incidence of CVD					
Low eGFR (eGFR < 60 mL/min per 1.73 m^2)	1.21	1.13–1.29	<0.0001	1.18	1.09–1.26	<0.0001
Proteinuria (+ or more)	1.33	1.21–1.46	<0.0001	1.19	1.05–1.35	0.01
Untreated HTN (SBP ≥ 140 or DBP ≥ 90 mmHg)	1.05	0.93–1.17	0.46	1.06	0.92–1.21	0.41
Treated HTN (SBP < 140 and DBP < 90 mmHg)	1.81	1.69–1.94	<0.0001	1.87	1.76–2.00	<0.0001
HTN with treatment (SBP ≥ 140 or DBP ≥ 90 mmHg)	1.56	1.45–1.68	<0.0001	1.61	1.49–1.73	<0.0001
Hypertriglyceridaemia (TG ≥ 200 mg/dL)	1.00	0.91–1.10	0.98	1.11	0.99–1.24	0.07
Hyper LDL (LDL ≥ 140 mg/dL)	1.04	0.97–1.12	0.24	0.94	0.88–1.01	0.11
Lower HDL (HDL ≤ 40 mg/dL)	1.00	0.77–1.30	0.99	1.00	0.81–1.25	0.98
Lipid-lowering drugs (yes)	1.22	1.13–1.32	<0.0001	1.17	1.10–1.24	<0.0001
Hyperglycaemia (FBS ≥ 126 mg/dL)	1.02	0.91–1.15	0.73	1.06	0.91–1.24	0.43
Hypoglycaemic drugs (yes)	1.26	1.14–1.40	<0.0001	1.26	1.12–1.42	<0.001
Smoking (current smokers)	1.00	0.94–1.07	0.99	1.15	1.02–1.30	0.03
Age (years)	1.06	1.05–1.06	<0.0001	1.07	1.07–1.08	<0.0001
BMI (+1 kg/m^2)	1.01	1.01–1.02	0.02	1.01	1.01–1.02	0.01
δGFR (–10% per year)	1.23	1.18–1.28	<0.0001	1.14	1.10–1.18	<0.0001

Multivariable adjusted hazard ratio for the incidence of stroke, cardiac events or both (CVD) in male and female subjects, respectively, is demonstrated. All variables without δGFR at the baseline year were applied. δGFR, annual change in eGFR; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBS, free blood sugar; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; HTN, hypertension; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides; UP, urinary protein.

Table 3 Baseline characteristics of the study population by annual change in eGFR

	Male			Female		
Annual change in eGFR (% per year)	−20 to −10	−10 to +10	+10 to +20	−20 to −10	−10 to +10	+10 to +20
Study size (person-years)	16 483	174 143	11 943	23 133	260 604	26 409
Age (years)	63.1	63.0	64.6	63.3	63.2	63.7
Systolic blood pressure (mmHg)	132.4	130.7	130.8	128.5	127.5	126.9
Diastolic blood pressure (mmHg)	78.8	78.3	78.3	75.0	74.8	74.5
Use of anti-hypertensive drugs (%)	30.2	27.4	30.0	27.0	24.5	25.6
Fasting blood glucose (mg/dL)	103.1	100.7	100.7	94.9	94.2	93.8
Use of hypoglycaemic drugs (%)	7.4	5.7	6.0	4.2	3.2	3.2
Triglycerides (mg/dL)	141.7	133.2	136.2	111.4	108.6	110.0
Low-density lipoprotein (mg/dL)	119.6	121.3	122.7	128.6	129.9	130.5
High-density lipoprotein (mg/dL)	56.9	57.4	57.0	65.4	65.6	65.6
Use of lipid-lowering drugs (%)	9.6	8.8	9.9	18.9	18.3	18.7
Smoking (%)	29.2	25.8	23.4	6.6	5.4	5.5
Body mass index (kg/m^2)	23.7	23.7	23.8	22.8	22.7	22.7
Proteinuria (+ or more, %)	7.7	6.0	7.1	4.1	3.1	3.5
Low eGFR (%)	8.5	15.9	32.3	5.9	10.8	24.1
Baseline estimated GFR (mL/min per 1.73 m^2)	80.7	74.6	64.8	82.2	75.5	67.9
Stroke (events)	252	1 671	151	228	1 752	235
(% per person-years)	1.53	0.96	1.26	0.99	0.67	0.89
Cardiac event (events)	442	3 048	290	424	3 460	395
(% per person-years)	2.68	1.75	2.43	1.83	1.33	1.50
CVD (events)	653	4 431	418	620	4 963	603
(% per person-years)	3.96	2.54	3.50	2.68	1.90	2.28

Population size, comorbid conditions, and incidence of stroke, cardiac events, or both are shown with categorization based on annual change in eGFR. An eGFR lower than 60 mL/min per 1.73 m^2 at the baseline year was defined as reduced eGFR. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; UP, urinary protein.

+20% in males (2.01%) or in females (0.81%) per 1.73 m^2 per year ($P = 0.37$ in males or $P = 0.38$ in females).

DISCUSSION

Proteinuria and reduced GFR are known to be associated with increased risk of CVD both in males and in females.[6,11] Consistent with this, our study population showed that both of these features are independent risk factors for the development of CVD, and that the new CKD category[15] is a good tool for identifying populations at high-risk for CVD in Japan. Moreover, we demonstrated that annual decline in eGFR is associated with increased risk of CVD independent of proteinuria or reduced eGFR. Some studies have demonstrated that annual decline or increment in GFR in the general populations might influence prognosis.[8–14] While the rate of overall survival was examined by other researchers,[8,10] we analyzed large study populations to show that serial measurement of both creatinine and proteinuria is better to predict the incidence of CVD. Actually, other reports showed that a decline in eGFR is a risk factor for the incidence of CVD, although these researchers did not examine proteinuria.[9,11–14] Representative studies such as 'The Cardiovascular Health Study', which evaluated a cohort of community-based older adults ($n = 4380$),[9,14] the 'Atherosclerosis Risk in Communities (ARIC) Study' with 13 029 participants,[11] a Taiwanese study with 17 026 participants,[12] and a study that used the US Veterans Affairs national database[13] did not report any data on proteinuria and albuminuria.

Changes in kidney function are thought to influence endothelial dysfunction and vascular damage and result in the occurrence of vascular events.[2,5,9,11] Our study did not reveal the reasons for the increase in CVD that followed impaired kidney function. However, the subpopulation with the rapid decline in eGFR showed higher systolic blood pressure, a higher rate of anti-hypertensive drug, hypoglycaemic drug, and/or lipid-lowering drug use, and a higher rate of smokers than the reference subpopulation (Table 3). This finding implies that hypertension, hyperglycaemia, poor lipid status, and smoking as well as impaired kidney function synergistically affect vascular function, resulting in the higher incidence of CVD observed in this study population. A limitation of our study is that our database did not contain information about the types of anti-hypertensive drugs such as renin-angiotensin-targeted drugs involving in the incidence of CVD.[21] Otherwise, it might be an explanation for the decline in eGFR that significantly higher rate of massive proteinuria (i.e. [2+] or more) in the subjects with rapidly decreasing eGFR. It suggests the existence of renal intrinsic diseases such as acute or chronic nephritis, or advancing diabetic nephropathy with nephrotic proteinuria.

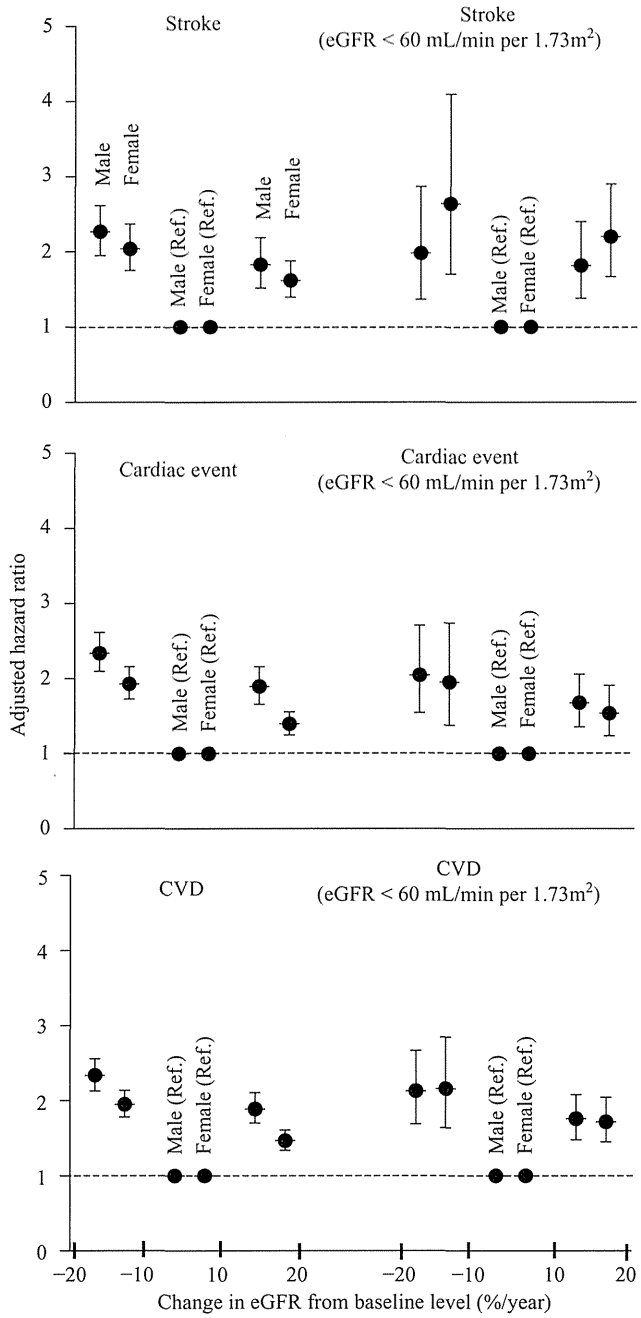

Fig. 2 Multivariable adjusted hazard ratio for the incidence of cardiovascular disease (CVD) in subpopulations based on annual change in estimated glomerular filtration rate (eGFR). The multivariable adjusted hazard ratio for the incidence of stroke, cardiac events, or both (CVD) in males and females is shown. Adjusted for age, body mass index, hypertension category, dyslipidaemia, taking anti-dyslipidaemia drugs, hyperglycaemia, taking hypoglycaemic drugs, reduced eGFR at baseline, proteinuria, and smoking. Error bars indicate 95% confidential intervals. CVD, cardiovascular diseases; eGFR, estimated glomerular filtration rate.

Some reports have demonstrated that an increase in eGFR is associated with excess mortality in the general population.[8,10] Although it is not easy to explain the involvement of increasing eGFR in the incidence of CVD, some researchers have mentioned that this phenomenon might be attributable to lower serum creatinine generation as a result of reduced muscle mass associated with chronic debilitating conditions.[13,22] Consistent with this perception, in our study population, a significantly negative correlation was found between the change in eGFR (+1% per year) and the change in BMI (−1 kg/m²) during the follow-up years ($r = -0.007$ and $P = 0.002$).

Although decline in eGFR is a known strong risk factor for the development of ESKD,[23] this study clarified that decline in eGFR is also important as a risk factor for the development of CVD. Therefore, our results suggest that decline in eGFR over time provides additional prognostic information regarding baseline eGFR in the Japanese general population. Our previous work demonstrated that CKD detection by using the urinary dipstick test and/or serum creatinine can be justified as a cost-efficient use of healthcare resources to help prevent the development of CKD, CVD, and death in populations with a high prevalence of the disease, such as those of Japan and other Asian countries.[24,25] Further socio-economical analysis is required to determine the cost-effectiveness of using the rate of annual decline in eGFR for detecting high risk of CVD and reducing the incidence of CVD.

To our knowledge, this is the first study to use a large-sized (over a 100 000 subjects) general population with sufficient available data including proteinuria to examine the incidence of CVD (i.e., stroke and cardiac events) and perform sub-analyses of the male or female subjects enrolled. These features allowed us to be the first to show that decline in eGFR is a risk factor in both males and females for the development of CVD in a community-based, frequent follow-up study, and that this risk factor is independent of proteinuria or reduced eGFR. However, this study also has several limitations. First, the information regarding incidence of CVD was obtained via a self-reported questionnaire. Second, measurement of biochemical parameters including proteinuria and serum creatinine was performed only once per year, and last, data about anti-hypertensive drugs are lacking.

Nevertheless, from this study, we can conclude that annual decline in eGFR is associated with an increased risk of CVD that is independent of proteinuria. Our study thus highlights a crucial role for annual serum creatinine measurement for the early detection of not only ESKD[23] but also CVD in the general population.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Characteristics of the study population, according to baseline urinary protein and estimated GFR.
Table S2 The incidence of CVD in the study population with categorized by according to CKD classification.
Fig. S1. Adjusted hazard ratio in male subjects for the incidence of CVD with categorized by CKD staging.
Fig. S2. Adjusted hazard ratio in female subjects for the incidence of CVD with categorized by CKD staging.
Fig. S3. Multivariable adjusted hazard ratio for the incidence of CVD by using baseline from −3% per year to +3% per year in eGFR.

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ORIGINAL ARTICLE

Comparison of predictive value for first cardiovascular event between Japanese GFR equation and coefficient-modified CKD-EPI equation

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Abstract
Background The most superior GFR-estimating equation from the viewpoint of cardiovascular disease (CVD) prediction remains unclear. Thus, we performed cross-sectional comparison between two GFR-estimating equations (Japanese GFR equation and coefficient-modified CKD-EPI equation) and CVD incidence using Japanese nationwide "specific health checkup" data.
Methods We recruited Japanese residents (241,159 individuals; mean 63 years; male, 38.6 %) who had not experienced CVD event (cardiac disease or stroke, or both). We calculated estimated GFR using two equations, and compared their predictive value for first symptomatic CVD event within 1 year.
Results Of all subjects, the mean GFR estimated by the Japanese GFR equation (JPN-eGFR) modified for Japanese was 75.83 ± 16.18 mL/min/1.73 m^2, and that by the coefficient-modified CKD-EPI equation (mCKDEPI-eGFR) was 76.39 ± 9.61 mL/min/1.73 m^2. Area under the receiver operating characteristics curves (95 % confidence intervals) for predicting CVD event by mCKDEPI-eGFR vs. JPN-eGFR were 0.596 (0.589–0.603) vs. 0.562 (0.554–0.569). Using mCKDEPI-eGFR, the crude odds ratio (OR) for CVD incident in the 4th quartile group was far more than double (OR 2.46, 95 % CI 2.29–2.66) that in the 1st quartile group. Using JPN-eGFR, the crude OR in the 4th quartile group was less than double (OR 1.61, 95 % CI 1.51–1.73) that in the 1st quartile group. However, such superior predictive value of mCKDEPI-eGFR disappeared after adjustment for confounding factors (age, gender, BMI, presence of proteinuria, hypertension, diabetes, dyslipidemia and current smoking).
Conclusion GFR estimated by the coefficient-modified CKD-EPI equation was more closely related to CVD incidence than that estimated by the Japanese GFR equation. However, it is possible that low mCKDEPI-eGFR also

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reflects some cardiovascular risk(s) other than kidney dysfunction.

Keywords Chronic kidney disease · Cardiovascular disease · General population · MDRD · CKD-EPI · Japanese GFR equation

Introduction

Accumulated evidence has revealed that kidney dysfunction predicts both cardiovascular morbidity and all-cause mortality of the general population, not only in the Western population [1], but also in the Eastern population [2, 3]. Kidney dysfunction is associated with low-grade inflammation, endothelial dysfunction [4], and oxidative stress [5], all of which are known as nontraditional cardiovascular risk factors. Accordingly, from the epidemiological viewpoint, the main aim in estimating kidney function, or glomerular filtration rate (GFR), is to predict future events such as cardiovascular disease (CVD).

To calculate estimated GFR, the Modification of Diet in Renal Disease (MDRD) Study equation is currently used worldwide. In Japan, not the original MDRD equation, but the Japanese GFR equation in which coefficient for age, gender and serum creatinine was directly derived from Japanese data is used nationwide [6]. However, in 2009 the chronic kidney disease epidemiology collaboration (CKD-EPI) proposed an alternative equation [7], which applies different coefficients to the same three variables used in the MDRD Study equation and Japanese GFR equation (age, gender, and serum creatinine level). The CKD-EPI equation was developed to provide a more accurate estimate of GFR among individuals with normal or only mildly reduced GFR (i.e., above 60 mL/min/1.73 m^2) [7]. Compared with the MDRD equation, the most different point of the CKD-EPI equation is the avoidance of overestimation among subjects with lower serum creatinine level (<0.7 mg/dL in female and <0.9 mg/dL in male). Although which of these two equations (or modifications thereof) is favored by a general practice is unclear [8], results of meta-analysis have recently been published showing that the predictive value of the CKD-EPI equation for CVD is superior to that of the MDRD equation [9]. Regarding the precise conditions regarding the issue of which GFR-estimating equation is superior in terms of CVD prevention, recent report from rural community in Iwate, Japan demonstrated the superiority of the CKD-EPI equation over Japanese GFR equation [10]. However, nationwide condition regarding this problem is not clear as yet.

The aim of this study was to prove which GFR-estimating equation is superior in terms of CVD prediction using national "specific health checkup" data. The present study provides us with information regarding the predictive values of each GFR-estimating equation among the Japanese general population.

Methods and subjects

The "Specific Health Checkup" system

The "Specific Health Checkup" system ("Tokutei-Kenshin" in Japanese) is a health checkup and guidance system for adult Japanese citizens and carried out nationwide annually. The system was initiated in April 2008 in Japan by the Ministry of Health, Labour and Welfare to detect metabolic syndrome, and if confirmed, to provide individual instructions to modify lifestyle and necessary treatment [11].

Study population ("Specific Health Checkup" participants)

Individual records of 1,030,679 participants who participated in the "Specific Health Checkup" in both 2008 and 2009 were anonymously provided and included in this study. Among these participants, those who had data for serum creatinine, age, gender, and body weight were selected, as serum creatinine test had not been mandatory. Data from the nationwide database was obtained for 24 prefectures (Hokkai-do, Yamagata, Miyagi, Ibaraki, Tochigi, Saitama, Tokyo, Kanagawa, Ishikawa, Niigata, Nagano, Gifu, Osaka, Okayama, Tokushima, Kochi, Fukuoka, Saga, Kumamoto, Nagasaki, Oita, Miyazaki, Okinawa, and Fukushima) that agreed with the study aims. Ethical approval was obtained from Fukushima Medical University (Accept No. 1485). Data were sent to a data center called the NPO Japan Clinical Research Support Unit to be verified. Outliers accounted for 0.01–0.1 % of the total and were treated with winsorization (Supplementary data; Table S1) [12]. Of the 1,030,679 participants in the databases, 765,653 were excluded due to missing serum creatinine level, gender, or past CVD history. We also excluded 23,867 people who already had experienced CVD in 2008. Thus, the present study comprised 241,159 subjects, representing 23.4 % of the residents who participated in the "specific health checkup" held in 2008 and 2009.

Eligible participants visited a pre-assigned clinic or hospital and responded to a questionnaire regarding past history of stroke and cardiac disease, and medications for hypertension, diabetes mellitus, and dyslipidemia. Physical measurements including height, weight and blood pressure were taken, and then blood samples were collected to