the economic model comparing do-nothing scenario with dipstick test only, serum Cr assay only, and both. The two policies were: mandate the use of serum Cr assay in addition to the current dipstick test (Policy 1); or mandate the use of serum Cr assay only and abandon dipstick test (Policy 2). Policy 1 meant that the current SHC practice, which was a mandatory 100 % use of dipstick test with 60 % use of serum Cr assay at discretion, would become a mandatory 100 % use of both dipstick test and serum Cr assay; while Policy 2 meant that the current practice would switch to the mandatory 100 % use of serum Cr assay and no use (0 %) of dipstick test. The latter assumption was made by the change in diagnosis criterion of diabetes [18], in which a blood test to check the level of haemoglobin A1c instead of a dipstick test to check urinary sugar level had become pivotal. And the model estimator comparing

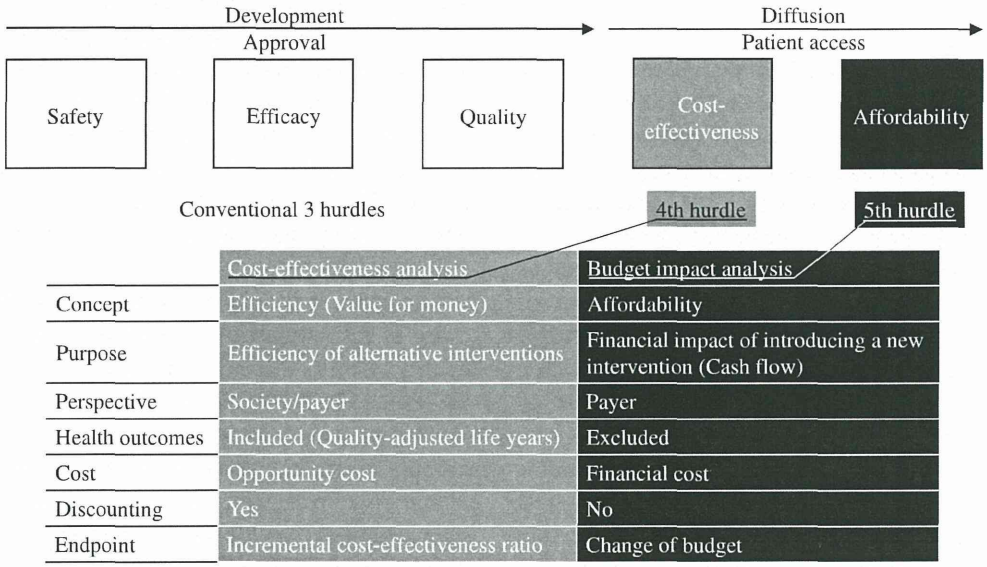


Fig. 1 In addition to conventional three hurdles for approval through development phase, two modern hurdles for patient access through diffusion phase are widely recognised these years: 4th hurdle for cost-effectiveness and 5th hurdle for affordability. These hurdles are appraised by cost-effectiveness analysis and budget impact analysis, respectively. Cost-effectiveness analysis concerns efficiency of resources use based on the valuations of cost and effectiveness at the same time comparing technical alternatives, while budget impact analysis concerns affordability of the government or the third party payer by demonstrating changes of cash flows as a result of making an intervention accessible for the population

Table 1 Summary of cost-effectiveness of chronic kidney disease (CKD) screening test in Japan

Objective The study aims to assess the cost-effectiveness of population strategy, i.e. mass screening, for CKD control and Japan's health checkup reform

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

Results Number of screened patients and incremental cost-effectiveness ratios (ICERs) of mass screening compared with do-nothing were calculated as 832 patients out of 100,000 participants and ¥1,139,399/QALY (US $12,660/QALY) for dipstick test only; 3,448 patients and ¥8,122,492/QALY (US $90,250/QALY) for serum Cr assay only; and 3,898 patients and ¥8,235,431/QALY (US $91,505/QALY) for both. Number of additionally screened patients and ICERs associated with the reform were calculated as 1,061 (3,898 from 2,837) patients out of 100,000 participants and ¥9,325,663/QALY (US $103,618/QALY) for mandating serum Cr assay in addition to the currently used mandatory dipstick test (Policy 1), and 611 (3,448 from 2,837) patients ¥9,001,414/QALY (US $100,016/QALY) for mandating serum Cr assay and applying dipstick test at discretion (Policy 2). The decrease of new haemodialysis patients compared with do-nothing in the fifth year and tenth year were estimated as 0.293 %/1.128 % for dipstick test only, 5.092 %/4.380 % for serum Cr assay only, and 5.094 %/4.380 % for both. The decrease of new haemodialysis patients associated with the reform was 1.249 %/1.346 % for Policy 1 and 1.251 %/1.346 % for Policy 2

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

Source Kondo et al. [12]

do-nothing scenario with dipstick test only scenario reflected the choice of continuing the current policy. Our budget impact analysis evaluated these policy options.

Health care budget impact is defined as a forecast of rates of use (or changes in rates of use) with their consequent short- and medium-term effects on budgets and other resources to help health service managers plan such changes [19]. We took the following three steps in our analysis: (1) the estimation of annual incremental budget per person, (2) the estimation of annual number of adults who would uptake SHC and (3) the estimation of budget impact by combining the results from (1) and (2).

The first step (1) was implemented on our economic model assuming that the annual economic model would be good for 15 years (Table 2). It included costs borne by adults and social insurers from the societal perspective, while costs of sectors other than health and productivity losses were uncounted. Costs expended by social insurers without discounting were counted as budgets. Costs for screening were fully borne by social insurers, and costs for further detailed examination and treatment at health facilities were 70 % reimbursed except in case of dialysis. Fixed co-payment for dialysis patients, ¥10,000 (US$100, US$1 =¥100) per month, was subtracted from the total cost. Assumed annual budgets per person are shown in Table 2.

In the second step (2), we used a population projection for Japan [20], and sex and age structure was applied to our annual economic model. We assumed that the uptake of SHC was fixed at 41.3 % for 15 years [21]. In the third step (3), estimated annual incremental budgets per person were multiplied by estimated annual number of adults who would uptake SHC.

Table 2 Assumptions for budget impact analysis

1. The annual economic model is good for 15 years	
2. Annual budgets per person (costs in the economic model [12])	
Screening	
Dipstick test only	¥ 267 (¥267)
Serum Cr assay only	¥138 (¥138)
Dipstick test and serum Cr assay	¥342 (¥342)
Detailed examination at clinic or hospital	¥17,500 (¥25,000)
CKD treatment	
Stage 1	¥84,000 (¥120,000)
Stage 2	¥102,900 (¥147,000)
Stage 3	¥235,900 (¥337,000)
Stage 4	¥555,100 (¥793,000)
Stage 5	¥691,600 (¥988,000)
ESRD treatment	¥5,880,000 (¥6,000,000)
Heart attack treatment	
1st year	¥1,946,000 (¥2,780,000)
2nd year and after	¥125,300 (¥179,000)
Stroke treatment	
1st year	¥700,000 (¥1,000,000)
2nd year and after	¥125,300 (¥179,000)
3. A population projection for Japan [17] is used and sex and age structure is applied for the annual economic model	
4. The uptake of SHC is fixed at 41.3 % for 15 years [18]	

Results

Table 3 shows the model estimators of budget impact. Compared with do-nothing scenario, total additional expenditure of dipstick test only decrease from ¥79 million (US$0.79 million) in the first year (2012) to ¥−1,067 million (US$−10.67 million) in the fifteenth year (2026); those of serum Cr assay only increase from ¥2,505 million (US$25.05 million) to ¥9,235 million (US$92.35 million); those of both dipstick test and serum Cr assay increase from ¥2,517 million (US$25.17 million) to ¥9,251 million (US$92.51 million); and those of status quo increase from ¥1,542 million (US$15.42 million) to ¥5,122 million (US$51.22 million). These estimators are also shown in Fig. 2. The breakdown of additional expenditures for screening and curative care is also reported in Table 3. Additional expenditures for screening are almost constant: ¥16 million (US$0.16 million) for dipstick test only, ¥8 million (US$0.08 million) for serum Cr assay only, ¥20 million (US$0.2 million) for dipstick test and serum Cr assay, and ¥18 million (US$0.18 million) for status quo. Decreases or increases during the 15 years are attributable to the changes in additional expenditure for curative care.

Table 4 shows the results of budget impact analysis in the same way focusing on the two policy options. Compared with status quo, the budget impacts as total additional expenditure of Policy 1 which requires serum Cr assay increase from ¥975 million (US$9.75 million) in the first year (2012) to ¥4,129 million (US$41.29 million) in the fifteenth year (2026); and those of Policy 2 which requires serum Cr assay and abandons dipstick test increase from ¥963 million (US$9.63 million) to ¥4,113 million (US$41.13 million). These are drawn in Fig. 3 as well. Breakdowns of screening and curative care are also reported in Table 4. Additional expenditures for screening are almost constant: ¥2 million (US$0.02 million) for Policy 1, and ¥−10 million (US$−0.1 million) for Policy 2. Increases during the 15 years are attributable to the changes in additional expenditure for curative care.

Discussion

We estimate the budget impacts of CKD screening test in SHC, of which use has been found cost-effective elsewhere [12]. With regard to two reform policy options: mandate

Table 3 Model estimators of budget impact

Year	Budget impact: total additional expenditure (¥, million)				Additional expenditure for screening (¥, million)				Additional expenditure for curative care (¥, million)			
	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo
1st (2012)	79	2,505	2,517	1,542	16	8	20	18	64	2,497	2,497	1,524
2nd (2013)	−96	3,295	3,308	1,946	16	8	20	18	−112	3,287	3,288	1,928
3rd (2014)	−278	3,972	3,985	2,280	16	8	20	18	−294	3,964	3,965	2,262
4th (2015)	−454	4,561	4,574	2,563	16	8	20	18	−470	4,553	4,554	2,545
5th (2016)	−615	5,089	5,103	2,815	16	8	20	18	−631	5,081	5,083	2,797
6th (2017)	−755	5,572	5,586	3,049	16	8	20	18	−771	5,564	5,566	3,031
7th (2018)	−872	6,025	6,039	3,274	16	8	20	18	−887	6,017	6,019	3,256
8th (2019)	−964	6,453	6,467	3,494	16	8	20	18	−979	6,445	6,447	3,476
9th (2020)	−1,032	6,861	6,875	3,712	16	8	20	18	−1,048	6,853	6,855	3,693
10th (2021)	−1,079	7,261	7,275	3,933	16	8	20	18	−1,094	7,252	7,255	3,915
11th (2022)	−1,105	7,660	7,675	4,162	16	8	20	18	−1,120	7,652	7,655	4,144
12th (2023)	−1,114	8,060	8,076	4,399	16	8	20	18	−1,129	8,052	8,056	4,380
13th (2024)	−1,109	8,456	8,472	4,638	16	8	20	18	−1,124	8,448	8,452	4,620
14th (2025)	−1,092	8,845	8,861	4,878	16	8	20	18	−1,108	8,837	8,841	4,860
15th (2026)	−1,067	9,235	9,251	5,122	16	8	20	18	−1,083	9,227	9,231	5,104

Cr creatinine

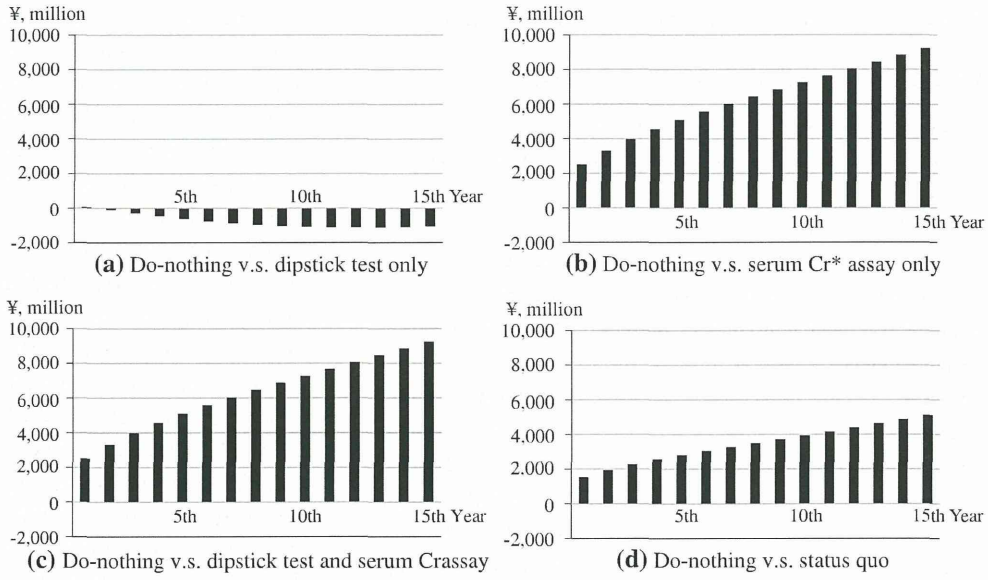


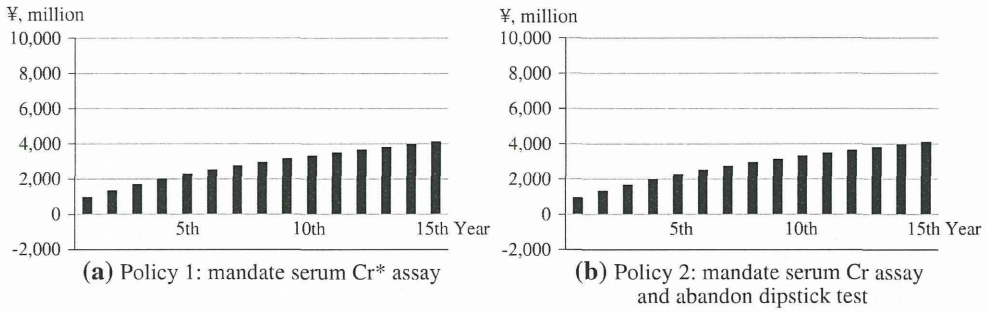
Fig. 2 *Black bars* depict annual budget impacts of mass screening compared with do-nothing scenario. Negative budget impacts on (**a**) imply that the continuation of current policy which mandates dipstick test only would contain medical care expenditure. **a** Do-nothing versus dipstick test only. **b** Do-nothing versus serum Cr assay only. **c** Do-nothing versus dipstick test and serum Cr assay. **d** Do-nothing versus status quo. *Cr* creatinine

serum Cr assay in addition to the dipstick test (Policy 1), and mandate serum Cr assay and abandon dipstick test (Policy 2), both positive and increasing budget impacts are found in the fifteen-year time frame. Although there is no established rule for interpreting the results of budget impact analysis, estimated values of ¥963 million (US$9.63 million) to ¥4,129 million (US$41.29 million) per year over fifteen years are considerable amounts of money of limited resources. These amount to 0.0026 to 0.011 % of national medical care expenditure in 2010 [22], and 0.068 and 0.29 % of the annual increase between 2009 and 2010, ¥1,413,500 million (US$14,135 million), respectively. Our case study exemplifies a situation where budgetary constraints, or affordability, matters to the use of

Table 4 Results of budget impact analysis

Year	Budget impact: total additional expenditure (¥, million)		Additional expenditure for screening (¥, million)		Additional expenditure for curative care (¥, million)	
	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test
1st (2012)	975	963	2	−10	973	973
2nd (2013)	1,362	1,349	2	−10	1,360	1,359
3rd (2014)	1,705	1,692	2	−10	1,704	1,702
4th (2015)	2,011	1,998	2	−10	2,010	2,008
5th (2016)	2,287	2,274	2	−10	2,285	2,284
6th (2017)	2,537	2,523	2	−10	2,535	2,533
7th (2018)	2,765	2,751	2	−10	2,763	2,761
8th (2019)	2,973	2,958	2	−10	2,971	2,969
9th (2020)	3,164	3,149	2	−10	3,162	3,159
10th (2021)	3,342	3,328	2	−10	3,341	3,338
11th (2022)	3,513	3,498	2	−10	3,511	3,508
12th (2023)	3,677	3,662	2	−10	3,675	3,672
13th (2024)	3,833	3,818	2	−10	3,832	3,828
14th (2025)	3,983	3,967	2	−10	3,981	3,977
15th (2026)	4,129	4,113	2	−10	4,127	4,123

Cr creatinine



(a) Policy 1: mandate serum Cr* assay

(b) Policy 2: mandate serum Cr assay and abandon dipstick test

Fig. 3 *Black bars* depict annual budget impacts associated with suggested mass screening policy reforms which mandate the use of serum Cr assay. Positive budget impacts on both panels imply that the reforms would result in the increase of medical care expenditure. **a** *Policy 1* mandate serum Cr assay. **b** *Policy 2* mandate serum Cr assay and abandon dipstick test. *Cr* creatinine

cost-effective interventions which have been judged as worth using according to social willingness to pay for new intervention.

The most impressive finding of this study, however, is the decreasing additional expenditures of dipstick test only scenario, which become negative in just its second year. This suggests that the mandatory dipstick test under current practice would contain medical care expenditure, i.e. 'decreasing annual national medical costs'. In other words, this is a valuable evidence that prevention saves life as well as money. And requiring dipstick test instead of serum Cr assay as a mandatory test item in SHC in 2008 may have been a sensible choice.

Due caution is needed to interpret the results of our budget impact analysis, since they depend on crucial assumptions. Positive budget impacts are found to be attributable to additional expenditure for curative care; however, for example, the analysis does not take medical advancement or health system development into account. In the coming 15 years, innovative therapeutic agents to prevent progression to ESRD are expected [23–26], and community-based CKD control intervention under collaboration between general practitioners and nephrologists is under study [27]. More prevention of ESRD should bring significant reduction in budget impact, since treatment of ESRD is most costly. With regard to the mass screening test, other

tests such as microalbuminuria or cystatin C could be an option in the middle to long run [24], which would fundamentally change the background of this analysis.

In the policy arena, the revision of SHC after its first five-year period was made in 2012, in which the continuation of current policy was chosen. And our study is in accord with keeping dipstick test in the mandatory test list. Further economic evaluation incorporating medical advancement or health system development is necessary for the future development of SHC and the next revision of CKD mass screening.

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

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ORIGINAL ARTICLE

An association between serum γ-glutamyltransferase and proteinuria in drinkers and non-drinkers: a Japanese nationwide cross-sectional survey

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Abstract

Background The association between alcohol consumption and chronic kidney disease (CKD), characterized by reduced glomerular filtration rate and proteinuria, is controversial. Recent studies suggest that serum γ-glutamyltransferase (GGT) level, a conventional marker of excessive alcohol consumption, predicts the CKD incidence. Little information is available on the difference in the clinical impact of alcohol consumption and GGT on proteinuria.

Methods The present cross-sectional survey included 332,296 Japanese people aged ≥40 years in 2008. To examine the associations of GGT and alcohol consumption with proteinuria, 134,600 men and 197,696 women were classified into 20 categories based on GGT quartiles and alcohol consumption categories, and their prevalence rate ratios (PRR) of proteinuria defined as ≥1+ of dipstick urinary protein were calculated after adjusting for clinically relevant factors.

Results Prevalence of proteinuria was 7.5 and 3.7 % in men and women, respectively. In both gender an association between alcohol consumption and proteinuria was in a J-shaped fashion with the lowest PRR of mild drinkers with ≤19 g/day of ethanol consumption, whereas an association between serum GGT level and proteinuria was linear. Compared with rare drinkers in the lowest GGT quartile, the subjects in higher GGT quartiles had a higher probability of proteinuria, irrespective of alcohol consumption. An optimal cutoff level of serum GGT was 43.6 and 23.2 IU/L in men and women, respectively.

Conclusions The subjects with higher serum GGT level had a higher probability of proteinuria, regardless of alcohol consumption, suggesting that GGT has a clinically greater impact on CKD than alcohol consumption.

Keywords Proteinuria · γ-Glutamyltransferase · Alcohol

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Introduction

Alcohol consumption is one of the main modifiable lifestyle factors associated with cardiovascular disease and its risk factors, including hypertension [1], diabetes [2–4],

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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