Table 1. Baseline characteristics of study participants with and without renal insufficiency

	Subjects without proteinuria	Subjects with proteinuria	Sixtiles of SBP (mm Hg) in the subjects with proteinuria						
			S1 (≦118)	S2 (119–127)	S3 (128–133)	S4 (134–140)	S5 (141–150)	S6 (≧151)	*P* value
Number	136,000	5,514	908	881	933	1,038	856	898	
Age (years)	62.9 ± 7.6	63.6 ± 7.8	59.2 ± 9.4	62.3 ± 8.4	63.8 ± 7.3	64.2 ± 6.8	64.2 ± 6.8	64.4 ± 6.8	<0.001
Male (%)	37.6	54.1*	49.0	52.4	53.7	56.9	57.9	54.2	0.002
Smoker (%)	13.3	20.7*	24.9	18.8	19.5	20.7	20.0	19.9	0.024
Alcohol consumption (%)	43.9	50.4*	45.8	48.5	47.9	55.1	53.6	51.2	<0.001
Obesity (%)	23.9	39.5*	20.3	34.9	40.1	45.6	45.7	49.7	<0.001
Body mass index (kg/m^2)	23.0 ± 3.2	24.3 ± 3.9*	22.4 ± 3.6	23.9 ± 3.5	24.5 ± 3.8	24.9 ± 3.7	25.0 ± 4.0	25.3 ± 3.9	<0.001
Systolic BP (mm Hg)	128.3 ± 17.2	134.7 ± 18.5*	108.3 ± 8.0	122.7 ± 2.5	130.2 ± 1.4	137.5 ± 2.3	146.1 ± 3.0	164.1 ± 12.0	<0.001
Diastolic BP (mm Hg)	75.9 ± 10.5	79.1 ± 11.3*	67.5 ± 7.9	74.6 ± 7.4	78.0 ± 7.8	80.4 ± 8.6	84.2 ± 9.0	90.1 ± 11.6	<0.001
eGFR (ml/min/1.73 m^2)	78.1 ± 13.2	78.0 ± 14.0	78.2 ± 13.2	78.8 ± 14.4	77.8 ± 13.8	77.9 ± 14.5	77.5 ± 13.5	78.1 ± 14.4	0.508
Triglyceride (mg/dl)	117.1 ± 76.1	136.9 ± 96.8*	116.7 ± 82.0	128.3 ± 78.7	139.0 ± 108.4	141.0 ± 101.2	147.2 ± 97.4	149.2 ± 104.3	<0.001
LDL cholesterol (mg/dl)	125.8 ± 29.7	125.4 ± 31.6	122.9 ± 30.9	125.2 ± 29.8	122.3 ± 31.0	128.1 ± 32.4	126.5 ± 31.3	127.5 ± 33.7	<0.001
HDL cholesterol (mg/dl)	62.7 ± 15.9	59.8 ± 16.3*	61.3 ± 16.8	59.9 ± 17.1	59.6 ± 17.2	59.3 ± 15.3	59.3 ± 16.3	59.7 ± 16.4	0.069
$HbA1_c$ (%)	5.3 ± 0.6	5.6 ± 1.1*	5.4 ± 1.0	5.5 ± 1.0	5.6 ± 1.0	5.7 ± 1.1	5.7 ± 1.0	5.8 ± 1.3	<0.001
Uric acid (mg/dl)	5.0 ± 1.3	5.5 ± 1.4*	5.1 ± 1.3	5.4 ± 1.3	5.5 ± 1.4	5.6 ± 1.4	5.6 ± 1.3	5.6 ± 1.4	<0.001
Hypertension (%)	41.8	63.0*	16.4	36.9	52.2	72.9	100	100	<0.001
Diabetes (%)	5.8	16.2*	10.1	12.5	14.3	19.5	18.2	22.1	<0.001
Dyslipidemia (%)	53.8	61.4*	49.5	60.6	60.9	66.1	66.9	64.4	<0.001
Hyperuricemia (%)	7.7	14.0*	9.0	11.5	15.0	16.0	15.0	16.9	<0.001
Antihypertensive medication (%)	25.7	43.3*	16.2	35.2	47.5	53.6	54.8	51.3	<0.001

Mean ± SD.
Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate.
**P* < 0.001.

Table 2. The correlation between systolic and diastolic blood pressures and the 2-year change of eGFR

	Unadjusted			Adjusted[a]		
	Coefficient	SE	*P* value	Coefficient	SE	*P* value
Subjects with proteinuria						
Systolic BP (per 10 mm Hg increase)	−0.646	0.089	<0.001	−0.592	0.116	<0.001
Diastolic BP (per 10 mm Hg increase)	−0.337	0.144	0.020	0.331	0.182	0.070
Subjects without proteinuria						
Systolic BP (per 10 mm Hg increase)	−0.221	0.017	<0.001	−0.151	0.023	<0.001
Diastolic BP (per 10 mm Hg increase)	−0.142	0.027	<0.001	0.071	0.036	0.047

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SE, standard error.

[a]Adjusted for gender, age, body mass index, eGFR, HbA1c, triglycerides, LDL-C, HDL-C, uric acid, smoking, alcohol consumption, and antihypertensive medication.

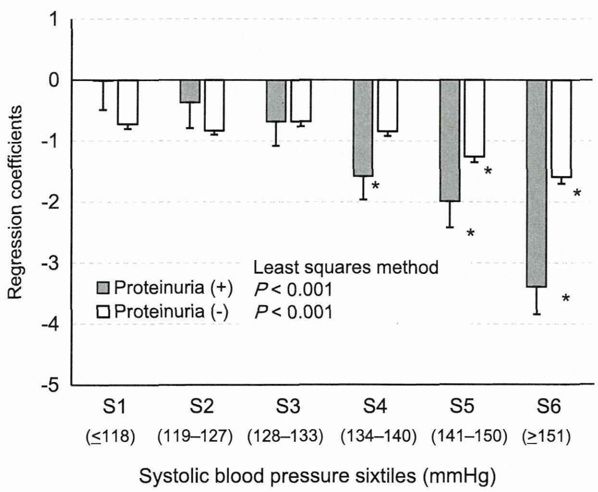

Figure 1. Systolic blood pressures at baseline and the 2-year change in the estimated glomerular filtration rates. Adjusted for sex, age, body mass index, diastolic blood pressure, estimated glomerular filtration rates, uric acid levels, glycated hemoglobin levels, triglycerides, low-density lipoprotein levels, high-density lipoprotein levels, smoking, alcohol consumption, and the use of antihypertensive medications at baseline. *$P < 0.05$ vs. the first sixtile (S1). Data are presented as the means (SE).

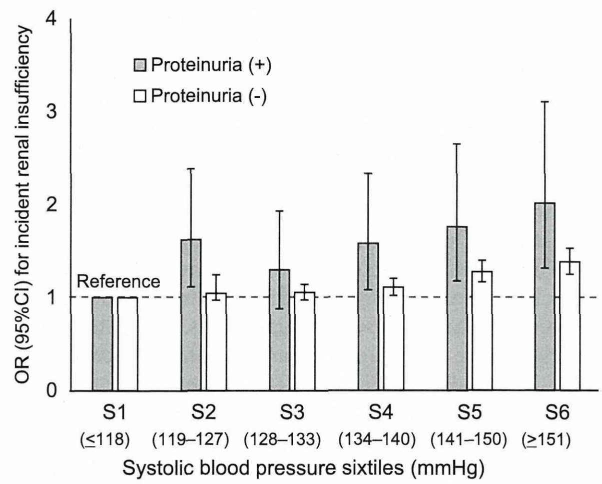

Figure 2. Odds ratios for systolic blood pressure levels in incident renal insufficiency. Adjusted for sex, age, obesity, diabetes, dyslipidemia, hyperuricemia, smoking, alcohol consumption, estimated glomerular filtration rates, diastolic blood pressure, and the use of antihypertensive medications at baseline. Abbreviations: CI, confidence interval; OR, odds ratio.

insufficiency. Therefore, the findings from this study appear to be robust. In addition, we studied a general Asian population that has not been investigated thoroughly in the past. Hence, the findings from this study might help to clarify the associations between blood pressure, proteinuria, and renal disease in Asian populations.

This study's results showed that a decline in renal function was significantly associated with a difference in the SBP, but not in the DBP. However, a large-scale study previously carried out on an Asian population presents the contradictory finding that an increase in DBP is an independent risk for renal events.[8] One possible explanation for this discrepancy might relate to the ages of the study participants, because those who participated in this study were older (mean age: 63 years) than those who participated in the previous study (mean age: 46 years), and sometimes low DBP levels within older populations reflect advanced arterial stiffness, which could be a risk factor associated with poor renal prognoses. Therefore, assessing and controlling SBP could be a practical approach towards the achievement of renoprotection in the general population, including older subjects.

The JNC-8 recommends maintaining SBP at <140 mm Hg and DBP at <90 mm Hg in patients with CKD.[1] In this study, a significant and rapid decline in the eGFR was observed at a lower SBP value in subjects with proteinuria (≥134 mm Hg) compared with subjects without proteinuria (≥141 mm Hg). Furthermore, the declines in the eGFRs were faster and the ORs for incident renal insufficiency were higher in subjects with proteinuria compared with those without proteinuria at the same SBP levels. We speculate that subjects with proteinuria have damaged glomeruli and that the increase in blood pressure accelerates the kidney damage. Our finding that subjects with higher grades of proteinuria showed faster eGFR declines in high SBP levels concurs with previously reported studies of populations with renal insufficiency.[18,19] These observations suggest that SBP levels must be more stringently controlled in subjects with proteinuria, e.g., maintaining SBP at <130 mm Hg, as recommended by the Japanese Society of Hypertension.[20]

In this study, subjects with proteinuria and low SBP levels of ≤118 mm Hg showed negligible declines in their eGFRs during the period of observation. The previously reported "J-curve phenomenon" in which low and high SBP levels are associated with faster declines in renal function in subjects with reduced renal function,[18] was not observed in this study. The reason for this discrepancy might be partly attributable to the fact that our results were obtained from an observational, rather than an interventional study, and the fact that we did not investigate a lower SBP category, e.g., <110 mm Hg.

SBP levels were inversely associated with changes in the eGFRs in the subjects without proteinuria, but the association of a difference in blood pressure was limited. The mechanism underlying renal function decreases in this population is unknown. If the main mechanism underlying such renal dysfunction does not include glomerular damage, but ischemia because of reductions in renal blood flows, lowering blood pressure might not be protective in this type of renal damage. This might explain why stringent blood pressure control did not result in the favorable outcomes that were reported for subjects with CKD[21] and older patients[22] with hypertension who underwent conventional blood pressure control.

The strength of this study lies in the large number of subjects who were distributed nationwide and were prospectively followed, which augments the robustness of our results. However, this study has several limitations. First, blood pressure levels were measured at baseline only; therefore, any changes in blood pressure that occurred during the follow-up period that might have an independent effect on renal outcomes were not evaluated. Second, the eGFRs were evaluated twice only, namely, at baseline and after 2 years. However, this parameter shows day-to-day variations, and measuring them twice only might underestimate the association between blood pressure and renal outcomes. Third, renal function was estimated using the Japanese equation for eGFR, rather than inulin clearance. Fourth, we have no information about the types of antihypertensive medications used by this population.

In conclusion, our study showed that SBP, but not DBP, was independently associated with a rapid decline in renal function in a community-based Japanese population, particularly in subjects with proteinuria. Subjects with proteinuria may require more stringent blood pressure control than those without proteinuria.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Significance of estimated glomerular filtration rate in predicting brain or heart attacks in obese and non-obese populations

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Abstract
Background The Japanese Specific Health Checkup mainly focuses on metabolic syndrome for preventing cardiovascular events. Subjects are stratified by measuring waist circumference, body mass index, blood pressure, triglycerides, and fasting plasma glucose. However, estimated glomerular filtration rate (eGFR) is not considered essential.
Methods A longitudinal cohort study assessed the association of eGFR with new-onset brain or heart attacks in a large Japanese nationwide Specific Health Checkup database. A total of 109,349 Japanese subjects (mean age 63.2 years, 39.5 % men) were examined for the events 2 years later. The odds ratios were calculated for new events in the total and subgroup populations divided by BMI < or ≥25 kg/m^2, obese and non-obese, respectively.
Results Obese subjects were more often male and had proteinuria (dipstick test ≥1+), lower eGFR, and higher systolic and diastolic BP, fasting plasma glucose, hemoglobin A1c, and triglycerides (TG). Rates of new-onset brain or heart attacks were 3.1 and 4.0 % in the groups of non-obese and obese subjects, respectively. In the total population, eGFR as well as higher BMI (≥25 kg/m^2), higher BP (high-normal hypertension or greater), higher TG (≥150 mg/dl), and proteinuria were significant risk factors for developing brain or heart attacks. The eGFR was significant in non-obese subjects, but not in the obese.
Conclusion As the ultimate aim of 'Specific Health Checkup' is to prevent cardiovascular events, our study suggests that eGFR should be evaluated in non-obese subjects.

Keywords Specific Health Checkup · Estimated GFR · Body mass index · Cardiovascular disease · Cerebrovascular disease

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Introduction

In Japan, lifestyle-related diseases account for 30 % of the national health expenditure and 60 % of the number of deaths from all causes [1]. The Japanese Ministry of Health, Labour and Welfare initiated the 'Specific Health Checkup' program in 2008, which focused on metabolic syndrome [2]. Its main purpose is to identify subjects at high risk of developing cardiovascular diseases, and then to intervene. Subjects requiring intervention are initially selected by their waist circumference, but the applied criterion is equivalent to a body mass index (BMI) of

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approximately 25 kg/m^2. Subjects are advised by a health nurse, the advice is called 'Specific Counseling Guidance' if they have a BMI of $\geq$25 kg/m^2, which is associated with blood pressure (BP) abnormality (systolic BP $\geq$130 mmHg or diastolic BP $\geq$85 mmHg), glucose intolerance (fasting plasma glucose [FPG] $\geq$ 100 mg/dl or HbA1c $\geq$ 6.0 %), or dyslipidemia (triglycerides [TG] > 150 mg/dl or high-density lipoprotein [HDL] cholesterol < 40 mg/dl). Checking proteinuria is essential, but is not included in the specific counseling guidance criteria. Measurements of serum creatinine and the estimated glomerular filtration rate (eGFR) are not essential, but some local governments have adopted the serum creatinine measurement.

In a cross-sectional study [3], eGFR was significantly correlated with the presence of past cardiovascular events, and a longitudinal study [4] reported that the annual change of eGFR was a risk factor for the incidence of cardiovascular events. Using the Specific Health Checkup data including the eGFR and BMI, we aimed to demonstrate the usability of eGFR to predict cardiovascular diseases.

Materials and methods

Study design and population

A total of 667,139 subjects received a health checkup in both 2008 and 2010, but subjects in 2009 were not used for our data set. Overall, 330,246 subjects were excluded in 2008 because of missing laboratory data such as eGFR or FPG, and 36,061 subjects were also excluded because of missing BP, BMI, and waist circumference data. Other 157,002 subjects were excluded in 2010 because of missing data on eGFR or urine dipstick results. A further 10,819 with a past history of a cardiac event, stroke, or kidney disease and 23,662 subjects with an unknown past history of brain or heart events were excluded in 2008 or 2010. The remaining 109,349 subjects were used in a longitudinal study.

The study 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. A new annual health check program, "The Specific Health Checkup", was started by the Japanese government in 2008, targeting early diagnosis and intervention for metabolic syndrome. The target population comprised Japanese citizens between the ages of 40 and 74 years. Local governments called for citizens to attend this annual health check under their own volition. Details, such as the participants' area of residence, have been reported previously [5].

This study was conducted according to the guidelines of the Declaration of Helsinki and was granted ethical approval by the ethics committee in Fukushima Medical University (No. 1485). Informed consent was not obtained from participants because all data were anonymized [6].

Baseline measurements

Blood samples were collected after an overnight fast and were assayed within 24 h with an automated clinical chemistry analyzer. Dipstick urinalysis was performed manually and results recorded as (−), (±), (1+), (2+), and (3+). In Japan, the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) recommends that all urine dipstick results of 1+ correspond to a urinary protein level of 30 mg/dl. Proteinuria was defined as 1+ or more. Because the dipstick test sometimes indicates microalbuminuria in the general Japanese population [7], a changeable urine concentration or protein other than albumin in urine should be considered. Therefore, we adopted a dipstick test of 1+ or more as reflecting positive urine protein. Glucose tolerance was categorized as normal glucose tolerance, prediabetes, or diabetes according to the new American Diabetes Association criteria [8]. Normal glucose tolerance was defined as HbA1c 5.7 % and FPG 100 mg/dl, prediabetes as HbA1c between 5.7 and 6.5 % or FPG between 100 and 125 mg/dl, and diabetes as HbA1c $\geq$ 6.5 % or FPG $\geq$ 126 mg/dl or taking anti-diabetes medication. Estimated GFR was derived using the following equation [9]:

$$\text{eGFR}\left(\text{mL/min/1.73m}^2\right) = 194 \times \text{age (years)}^{-0.287} \times \text{serum creatinine (mg/dl)}^{-1.094}(\text{if female} \times 0.739).$$

In accordance with the recommendations of the Japanese Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured on the right arm using a standard sphygmomanometer or an automated device after resting for 5 min in a seated position. BP data were categorized as normal (systolic BP < 130 mmHg and diastolic BP < 85 mmHg), high-normal (systolic BP 130–139 mmHg or diastolic BP 85–89 mmHg), or hypertensive (systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, or taking BP medication).

All subjects completed a self-administered questionnaire to document their medical history and current medications. Information obtained included brain attacks such as brain infarction and hemorrhage, and heart events which included myocardial infarction and cardiac angina. We identified the subjects with new-onset brain or heart attacks as those who had a positive record of these events in 2010 but a negative record of both events in 2008. The study physicians performed a physical examination of each subject and rechecked their medical history to confirm the precision of the information. Body height and weight were measured in light clothing without shoes, and the BMI was calculated (kg/m^2).

Statistical analysis

All statistical analyses were performed with SPSS version 20.0J software (SPSS, Chicago, IL, USA). Data are expressed as mean ± SD. Clinical parameters and BP or metabolic values according to the BMI were compared using the Mann–Whitney *U* test, and categorical parameters were compared using the Chi squared test. Univariable and multivariable logistic regression analyses were used to examine the independent association of the level of eGFR with new-onset brain or heart attacks. In the multivariable analysis, associations were assessed with adjustments for age, sex, proteinuria, BMI, TG, and FPG, among others. Statistical significance was defined as $p < 0.05$.

Results

Correlation between BMI and new-onset brain or heart attacks

The distribution and prevalence of new-onset brain or heart attacks for each BMI category are shown in Fig. 1. The results show that the prevalence of new-onset brain or heart attacks increased according to an increase in BMI. However, the actual number of new-onset brain or heart attacks is higher in those with a BMI <24.5 kg/m^2 than ≥24.5 kg/m^2.

Comparison between subjects with BMI ≥ and < 25 kg/m^2

Subjects were divided into two groups, obese and non-obese, according to BMI < or ≥25 kg/m^2, respectively (Table 1). Age did not differ significantly between the groups. Among obese subjects, male sex and proteinuria (dipstick test ≥1+) were common. Compared with the non-obese subjects, obese subjects showed lower eGFR, higher systolic and diastolic BP, higher FPG, higher HbA1c, and higher TG.

The rates of new-onset brain or heart attacks were 3.1 and 4.0 % in the non-obese and obese subjects, respectively (Fig. 2). Chronic kidney disease (CKD) stages were classified as eGFR levels [9]; CKD stage G2 was set as a reference when multivariate logistic analysis was performed (Table 2). In the total population, stage G3a or G3b+ was a significant risk factor for CKD in a step-by-step manner. In the non-obese population, stage G3a or G3b+ was also significant. However, in the obese population, stage G1 or G3b+ was significant but not in stage G3a.

The multivariate logistic analysis data, except for the results of basal eGFR stratification, are shown in Table 2. The 2-year change of eGFR, male, older age, proteinuria, and higher BMI, BP, and TG levels were significant. In obese subjects, high-normal BP or worse was also a significant risk factor, while higher TG (≥150 mg/dl) and higher FPG (≥100 mg/dl) were not statistically significant, but their odds ratios were greater than one.

To clarify the significance of eGFR, the odds ratio of eGFR for new-onset brain or heart attacks was analyzed in incremental steps (Fig. 3). Estimated GFR was a significant risk factor for unadjusted analysis. In particular, the eGFR in the non-obese population remained significant after adjustment by age, sex, basal proteinuria, systolic BP, TG, low-density lipoprotein, and FPG, but was not significant in obese subjects.

Synergistic effect of eGFR and hypertension on brain or heart attacks differs according to BMI

Because high-normal BP or hypertension was found to be a strong risk factor, we checked the synergistic effect of

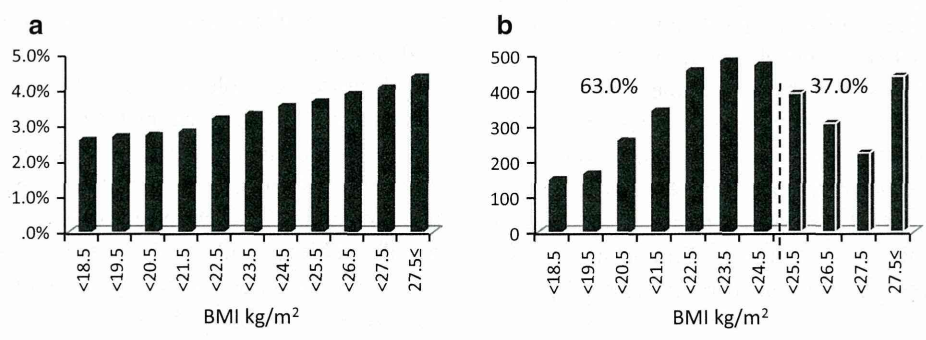

Fig. 1 Distribution of new-onset brain or heart attacks for each BMI category. **a** Prevalence or the affected number of new-onset brain or heart attacks. **b** The actual number of new-onset brain or heart attacks is higher in those with a BMI 24.5 kg/m^2 than ≥24.5 kg/m^2. The percentage of affected subjects with a BMI less than and more than 24.5 kg/m^2

Table 1 Population characteristics divided by BMI of and ≥25 kg/m²

	BMI < 25 kg/m²	BMI ≥ 25 kg/m²	Total	*p* value
Number of subjects	81,013	28,336	109,349	
BMI (kg/m²)	21.75 (2.03)	27.32 (2.27)	23.20 (3.22)	
Age (years)	63.2 (7.5)	63.2 (7.6)	63.2 (7.5)	0.260
Male, *n* (%)	29,918 (36.9 %)	13,288 (46.9 %)	43,206 (39.5 %)	<0.001
Height (cm)	156.9 (8.3)	157.1 (8.9)	157.0 (8.5)	0.003
Weight (kg)	53.8 (7.9)	67.6 (9.2)	57.4 (10.2)	<0.001
Waist circumference (cm)	80.4 (7.1)	92.9 (6.9)	83.6 (8.9)	<0.001
Serum creatinine (mg/dl)	0.71 (0.17)	0.74 (0.19)	0.71 (0.17)	<0.001
Basal eGFR, ml/min/1.73 m²	75.1 (14.9)	73.8 (15.3)	74.8 (15.0)	<0.001
Basal dipstick proteinuria (≥1+), *n* (%)	2,859 (3.5 %)	2,064 (7.3 %)	4,923 (4.5 %)	<0.001
SBP (mmHg)	127.3 (17.4)	133.9 (16.5)	129.0 (17.4)	<0.001
DBP (mmHg)	75.4 (10.5)	79.6 (10.3)	76.5 (10.6)	<0.001
BP, SBP ≥130 or DBP ≥85 or Drug, *n* (%)	42,694 (52.7 %)	20,793 (73.4 %)	63,487 (58.1 %)	<0.001
FPG (mg/dl)	95.7 (17.1)	101.8 (21.5)	97.3 (18.6)	<0.001
HbA1C (%)	5.68 (0.55)	5.87 (0.72)	5.73 (0.61)	<0.001
FPG, ≥100 or drug, *n* (%)	21,372 (26.4 %)	11,954 (42.2 %)	33,326 (30.5 %)	<0.001
TG (mg/dl)	107.8 (68.5)	136.7 (84.6)	115.3 (74.1)	<0.001
TG, ≥150 or drug, *n* (%)	22,904 (28.3 %)	12,317 (43.5 %)	35,221 (32.2 %)	<0.001

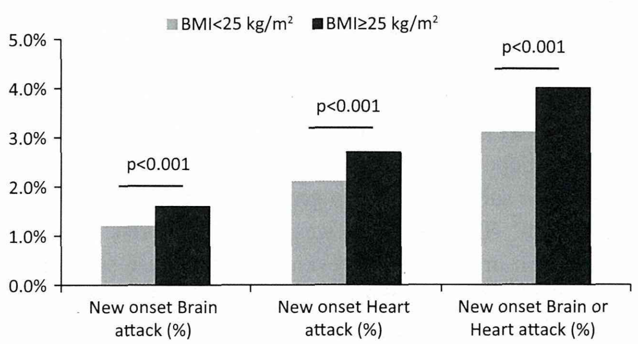

Fig. 2 Incidence of brain or heart attacks during follow-up. The rates of new-onset brain and heart attacks in non-obese and obese populations are shown. All three sets of differences were statistically significant

eGFR with BP levels. When both eGFR and BP were divided into CKD stages and BP categories, respectively, the odds ratio of each combination was calculated in a multivariate fashion adjusted by age (+5 years), sex (male vs. female), basal proteinuria (dipstick ≥1+), TG (≥150 or taking medication), and FPG (≥100 or taking medication). When the combination of 60–89 ml/min/1.73 m² of eGFR and normal BP was set as the reference, the odds ratios increased with decreasing eGFR and increasing BP categories, particularly in non-obese subjects. However, these relationships were not found in obese subjects. We confirmed that eGFR was still a significant risk factor and its power was strengthened when combined with BP in non-obese subjects (Fig. 4).

Discussion

The main conclusion from this study is that the health nurse intervention criteria of the 'Specific Counseling Guidance' generally seem to be appropriate. However, as the ultimate aim of the 'Specific Health Checkup' is to prevent cardiovascular events, eGFR measurement, particularly in non-obese subjects, as well as proteinuria should be included in the criteria.

The primary purpose of the 2008 Specific Health Checkup was to identify the high-risk cardiovascular subjects, and then to intervene via the Specific Counseling Guidance, also called 'Metabolic Syndrome Checkup', to reduce future cardiovascular events. Measurement of urine protein is also listed as being necessary, but is not included in the Specific Counseling Guidance criteria. However, CKD has recently become well known as a strong risk factor for the future development of cardiovascular events [10], but the measurement of eGFR is not recommended in this health checkup system as its value is not readily understood.

Table 2 Adjusted odds ratios of basal eGFR stratification (chronic kidney disease stages) for new-onset brain or heart attacks in the 2008–2010 longitudinal study

	Total population			BMI <25 kg/m^2			BMI ≥25 kg/m^2		
	OR	95 % CI		OR	95 % CI		OR	95 % CI	
Basal eGFR stratification (ml/min/1.73 m^2)									
eGFR ≥ 90 (stage G1)	1.040	0.943	1.148	0.981	0.872	1.104	**1.197**	1.003	1.429
60≤ eGFR <90 (stage G2)	1			1			1		
45≤ eGFR <60 (stage G3a)	**1.174**	1.072	1.286	**1.191**	1.065	1.332	1.147	0.979	1.344
eGFR < 45 (stage G3b or worse)	**1.751**	1.398	2.193	**1.515**	1.109	2.069	**2.105**	1.516	2.922
2-year eGFR change, −10 ml/ml/1.73 m^2	**1.105**	1.043	1.170	**1.126**	1.050	1.207	1.061	0.959	1.175
Male vs. female	**1.434**	1.339	1.536	**1.431**	1.317	1.551	**1.451**	1.282	1.642
Age, +5 years	**1.300**	1.264	1.337	**1.300**	1.256	1.345	**1.303**	1.240	1.369
Basal proteinuria	**1.356**	1.190	1.546	**1.446**	1.218	1.718	**1.245**	1.018	1.522
BMI, ≥25 vs.<25 kg/m^2	**1.129**	1.048	1.215						
BP, SBP ≥130 or DBP ≥85 or Drug	**1.513**	1.401	1.633	**1.527**	1.400	1.667	**1.468**	1.251	1.722
TG, ≥50 or drug	**1.080**	1.007	1.159	1.074	0.985	1.171	1.093	0.969	1.233
FPG, ≥100 or drug	1.026	0.955	1.102	0.994	0.909	1.086	1.089	0.965	1.229

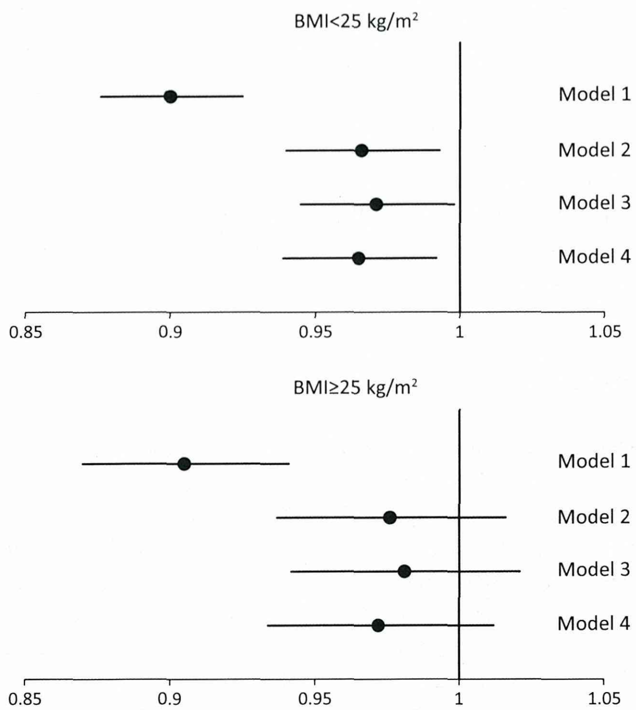

Fig. 3 Odds ratios of basal eGFR (+10 ml/min/1.73 m^2) for new-onset brain or heart attacks in non-obese (BMI <25 kg/m^2) and obese subjects (BMI ≥25 kg/m^2). Odds ratios of basal increment of eGFR (+10 ml/min/1.73 m^2) for new-onset brain or heart attack events were analyzed in a step-by-step manner. In non-obese subjects (*upper panel*), eGFR was a significant factor with not only unadjusted but also multivariate adjustment. In obese subjects (*lower panel*), eGFR was not significant when multivariate analysis was applied. Model 1, unadjusted, Model 2, model 1+ age, sex, Model 3, model 2+ basal proteinuria, Model 4, model 3+ systolic BP, TG, low-density lipoprotein, and FPG

Therefore, the aim of this study was to check the adequacy of these criteria using a large Japanese nationwide database. According to our data, the criteria for BMI, BP, and TG were verified as significant predictors of brain or heart attacks. The criterion of higher FPG was not significant, but had a tendency of predicting future brain or heart attack events. Proteinuria was shown to be an independent and strong significant risk factor for brain or heart attacks, and therefore, it should be added to the criteria.

Estimated GFR, calculated from serum creatinine, was also an independent risk factor in the total population. We divided the subjects into two groups using a BMI threshold of 25 kg/m^2. Though eGFR was a significant risk factor for future brain or heart attack events in non-obese subjects, it was not significant in obese ones. From these observations, assessing eGFR in obese subjects appears to be unnecessary. However, since the aim of the Specific Health Checkup is to prevent future brain or heart attack events, the measuring of eGFR should be recommended, particularly in the non-obese population.

Our study evaluated the usability of eGFR for predicting brain or heart attacks compared with using CKD stage G2. In a step-by-step manner, this CKD stage showed a worse odds ratio for brain or heart attack events in non-obese subjects. In obese subjects, however, CKD stage G3a compared with G2 was not significant, but stage G3b or worse was significant. It is unclear why stage G3a was not a risk factor in obese subjects, but possible explanations are (1) in obese subjects, there are some unknown but strong risk factors related to brain or heart attacks, such as adiponectin [12], resistin [12], and tumor necrosis factor

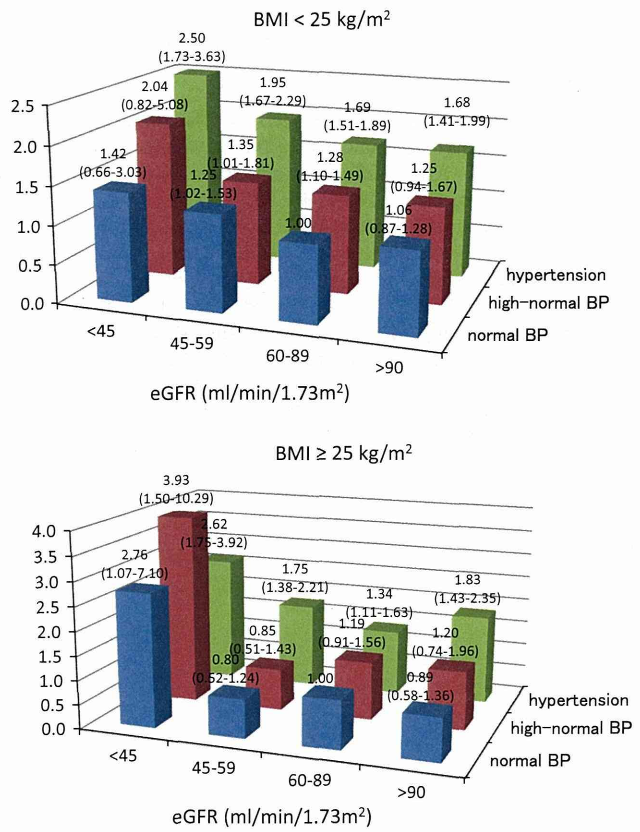

Fig. 4 Odds ratios for new-onset brain or heart attacks at combined levels of eGFR and BP in non-obese (BMI <25 kg/m^2) and obese populations (BMI ≥25 kg/m^2). When both eGFR and BP were divided in the chronic kidney disease (CKD) stages and BP categories, respectively, the odds ratios of each combination were calculated in a multivariate fashion adjusted by age, sex, basal proteinuria, TG abnormality, and glucose abnormality. The combination of 60–89 ml/min/1.73 m^2 of eGFR and normal BP was set as the reference. The odds ratios increased with decreasing eGFR and increasing BP categories in subjects with a BMI less than 25 kg/m^2 (*upper panel*). In subjects with a BMI of 25 kg/m^2 or more (*lower panel*), this relationship is unclear. Given numbers were odds ratio and 95 % confidence intervals

[13], and (2) subjects with higher BMI tend to have larger muscle mass, resulting in higher serum creatinine and lower calculated eGFR. This is because the eGFR equation does not include body weight [9], and therefore, some higher BMI subjects were included in CKD stage G3a even though their kidney function was in the normal range. Furthermore, stage G1 was also significant compared with stage G2 in obese subjects. In obese subjects, stage G1 refers to a hyperfiltration state, which has been reported as a risk factor for developing proteinuria [14] [15]. Therefore, the subsequent development of brain or heart attacks can be easily understood.

Among the criteria used in the Specific Counseling Guidance, higher BP had the strongest risk. To check the effect of combined eGFR and higher BP, we found a synergistic and stepwise effect between the two in non-obese subjects, but not in obese ones. Again, this finding supports the importance of eGFR in predicting brain or heart attacks.

The limitations in this study include possible biases toward recruiting participants who were particularly motivated to undergo a health examination, and also in the many subjects who were excluded because of missing data. Another limitation was the urine dipstick analyses which were performed manually. In addition, the BMI threshold was set at 25 kg/m^2, even though this variable shows some gender difference [5].

In conclusion, the criteria used for the health nurse intervention as specified in the 'Specific Counseling Guidance' seem appropriate in an obese population (BMI $\geq$ 25 kg/m^2). However, as the ultimate aim of the 'Specific Health Checkup' (Japanese name: Tokutei Kenshin) is to prevent cardiovascular events, eGFR should be evaluated in non-obese subjects with a BMI < 25 kg/m^2.

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Conflict of interest All the authors declare no competing interests.

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