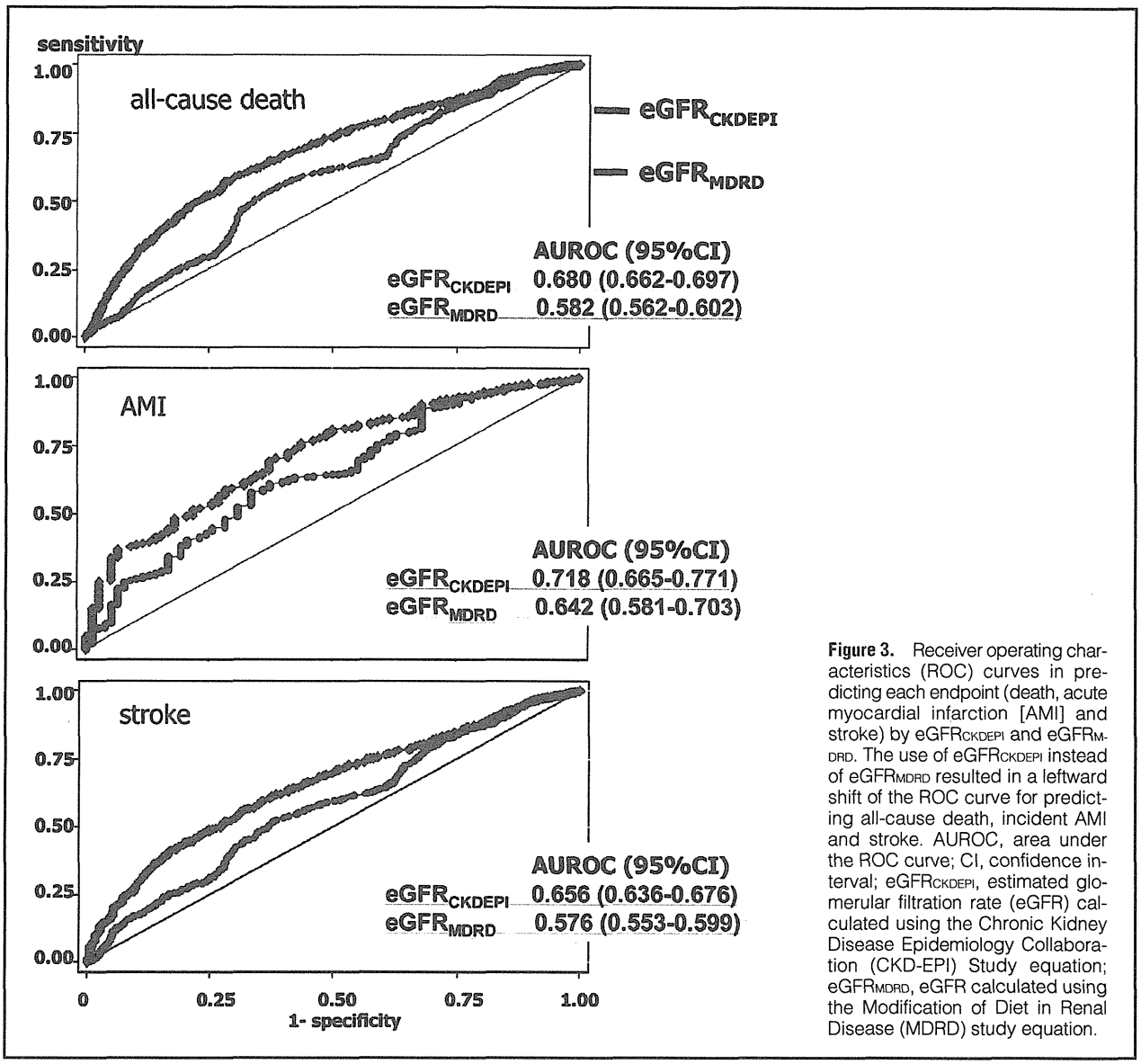

Figure 3. Receiver operating characteristics (ROC) curves in predicting each endpoint (death, acute myocardial infarction [AMI] and stroke) by $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$. The use of $eGFR_{CKDEPI}$ instead of $eGFR_{MDRD}$ resulted in a leftward shift of the ROC curve for predicting all-cause death, incident AMI and stroke. AUROC, area under the ROC curve; CI, confidence interval; $eGFR_{CKDEPI}$, estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study equation; $eGFR_{MDRD}$, eGFR calculated using the Modification of Diet in Renal Disease (MDRD) study equation.

of subjects in stage 1 (eGFR $\geq 90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) and in 7% of subjects in stage 2 ($69–89\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) using $eGFR_{CKDEPI}$ as the gold standard, while $eGFR_{MDRD}$ was overestimated in 13% of subjects in stage 2. Subclassification and age-stratification of CKD stage showed that significantly different age distributions between corresponding CKD stage based on $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$ contributed to over/underestimations. We have already listed the concordance/discordant results of CKD stage in detail elsewhere.[32]

Table 1 lists baseline characteristics vs. CKD stage based on $eGFR_{CKDEPI}$ and on $eGFR_{MDRD}$, and also the differences in baseline characteristics in each CKD stage between the models using $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$. Age distributions were very different between the 2 models. In stage 1 (eGFR $\geq 90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$), mean age was 43.0 years and had a narrow distribution in the $eGFR_{CKDEPI}$ model, while it was 56.2 years with a wide distribution in the $eGFR_{MDRD}$ model. The difference in mean age in CKD stage 1 was >13 years. Higher age with a narrower age distribution was observed in CKD stage 3a and stage 3b+ in the $eGFR_{CKDEPI}$ model compared to the $eGFR_{MDRD}$ model.

After completion of 5-year follow-up, the observed patient-years were 136,961. The mean follow-up period was 5.6 years. There were 851 deaths, 78 cases of AMI and 605 cases of stroke during the observation period. **Table 2** lists baseline characteristics of participants stratified by endpoint. The mean age of subjects who died during the observation period was 71.3 years, which was 10 years older than that of subjects who survived without events. The mean age of subjects in whom AMI or stroke occurred was approximately 70 years, which was 9 years older than that of survivors with no events. For the total subjects, differences in prevalence of CKD stage between $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$ were large in stage 1 (10.2% vs. 18.1%, χ^2=633, P<0.001) and stage 2 (83.9% vs. 69.7%, χ^2=1,382, P<0.001). The proportion of subjects with eGFR $<60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ was 5.9% for $eGFR_{CKDEPI}$ and 12.1% for $eGFR_{MDRD}$ (χ^2=584, P<0.001).

Figure 3 shows ROC curves for predicting each endpoint

Table 3. Events (Death or Incidence) and Mortality/Incidence Rates vs. eGFR

CKD stage (ml·min^{-1}·1.73 m^{-2})	eGFR ≥90	60≤eGFR<90	45≤eGFR<60	eGFR <45
CKD-EPI equation (n)	2,504	20,607	1,259	190
Death				
No. events (crude)	26 (1.86)	695 (6.04)	96 (14.0)	34 (33.4)
Sex- and age-adjusted (95% CI)	6.68 (4.05–9.30)	3.03 (2.66–3.41)	3.26 (2.43–4.08)	6.65 (4.14–9.16)
Multivariate-adjusted (95% CI)	7.21 (4.32–10.1)	3.70 (3.17–4.23)	4.09 (3.01–5.16)	7.50 (4.62–10.4)
AMI				
No. events (crude)	1 (0.07)	62 (0.54)	14 (2.06)	1 (0.98)
Sex- and age-adjusted (95% CI)	0.18 (0.00–0.53)	0.34 (0.22–0.47)	0.72 (0.22–1.23)	0.31 (0.00–0.95)
Multivariate-adjusted (95% CI)	0.15 (0.00–0.45)	0.27 (0.14–0.40)	0.50 (0.11–0.89)	0.19 (0.00–0.58)
Stroke				
No. events (crude)	11 (0.79)	521 (4.58)	61 (9.14)	12 (12.1)
Sex- and age-adjusted (95% CI)	2.27 (0.91–3.64)	2.92 (2.54–3.30)	3.19 (2.23–4.15)	3.71 (1.50–5.92)
Multivariate-adjusted (95% CI)	2.61 (1.03–4.20)	3.56 (2.99–4.12)	4.01 (2.75–5.27)	4.17 (1.66–6.69)
MDRD equation (n)	4,449	17,128	2,711	272
Death				
No. events (crude)	112 (4.47)	568 (5.95)	132 (8.88)	39 (26.6)
Sex- and age-adjusted (95% CI)	4.21 (3.40–5.02)	3.04 (2.65–3.43)	3.02 (2.38–3.66)	6.46 (4.19–8.73)
Multivariate-adjusted (95% CI)	4.80 (3.82–5.78)	3.73 (3.18–4.27)	3.79 (2.94–4.64)	7.36 (4.72–10.0)
AMI				
No. events (crude)	5 (0.20)	48 (0.50)	24 (1.62)	1 (0.68)
Sex- and age-adjusted (95% CI)	0.21 (0.02–0.39)	0.32 (0.20–0.45)	0.77 (0.35–1.19)	0.26 (0.00–0.80)
Multivariate-adjusted (95% CI)	0.17 (0.01–0.33)	0.26 (0.13–0.39)	0.56 (0.20–0.92)	0.17 (0.00–0.52)
Stroke				
No. events (crude)	69 (2.77)	428 (4.53)	94 (6.43)	14 (9.76)
Sex- and age-adjusted (95% CI)	2.81 (2.13–3.48)	2.88 (2.49–3.26)	2.89 (2.19–3.59)	3.25 (1.46–5.04)
Multivariate-adjusted (95% CI)	3.19 (2.37–4.00)	3.56 (2.98–4.14)	3.64 (2.70–4.59)	3.68 (1.63–5.72)

Crude, crude mortality/incidence rates; multivariate-adjusted, multivariate-adjusted mortality/incidence rates (/1,000 person-years); sex- and age-adjusted, sex- and age-adjusted mortality/incidence rates (/1,000 person-years). Multivariate adjustment for risk factors: age, SBP, BMI, TC, HDLC, HbA_{1c}, smoking habit and regular drinking habit.
CI, confidence interval. Other abbreviations as in Table 1.

Table 4. Adjusted HR (95% CIs) for Endpoint According to eGFR Type

CKD stage (ml·min^{-1}·1.73 m^{-2})	eGFR ≥90	60≤eGFR<90	45≤eGFR<60	eGFR <45	Model parameters in multivariate-adjusted Cox regression analysis		
Estimated using CKD-EPI equation							
Subjects	2,504	20,607	1,259	190	AIC	BIC	Harrell's C
Death	1.93 (1.25–2.98)	Ref	1.12 (0.90–1.40)	2.05 (1.43–2.92)	15,858	15,947	0.739
AMI	0.55 (0.07–4.34)	Ref	1.86 (1.01–3.44)	0.71 (0.10–5.24)	1,449	1,538	0.790
Stroke	0.72 (0.38–1.36)	Ref	1.13 (0.86–1.48)	1.17 (0.66–2.10)	11,441	11,530	0.729
Estimated using MDRD equation							
Subjects (n)	4,449	17,128	2,711	272	AIC	BIC	Harrell's C
Death	1.28 (1.04–1.58)	Ref	1.03 (0.85–1.25)	1.99 (1.43–2.78)	15,863	15,952	0.737
AMI	0.65 (0.25–1.67)	Ref	2.14 (1.29–3.55)	0.65 (0.09–4.78)	1,446	1,536	0.797
Stroke	0.89 (0.68–1.15)	Ref	1.02 (0.82–1.28)	1.03 (0.00–0.45)	11,442	11,531	0.729

Data given as multivariate-adjusted HR (95% CI). Adjustment for risk factors: age, sex, SBP, BMI, TC, HDLC, HbA_{1c}, existence of albuminuria, smoking habit, regular drinking habit and exercise habit.
AIC, Akaike's information criterion; BIC, Baysian information criterion; Harrell's C, Harrell's concordance statistics; HR, hazard ratio. Other abbreviations as in Tables 1,2.

according to eGFRCKDEPI and eGFRMDRD. The use of eGFRCKDEPI instead of eGFRMDRD results in a leftward shift of the ROC curve in prediction of all-cause death, incident AMI and stroke. AUROCs (95% confidence interval [95% CI]) for eGFRCKDEPI vs. eGFRMDRD were 0.680 (0.662–0.697) vs. 0.582 (0.562–0.602) in predicting all-cause death, 0.718 (0.665–0.771) vs. 0.642 (0.581–0.703) in predicting AMI and 0.656 (0.636–0.676) vs. 0.576 (0.553–0.599) in predicting stroke.

Table 3 lists number of events (death, AMI and stroke) and crude mortality and incidence rates, sex- and age-adjusted and multivariate-adjusted mortality and incidence rates, and their 95% CI (expressed as /1,000 person-years) in the 4 categories separately for the 2 models based on eGFRCKDEPI and on eGFRMDRD. A clear steep linear relationship between eGFR

Table 5. Reclassification of eGFR Categories According to Endpoint

CKD stage	eGFR$_{CKDEPI}$				Total
	eGFR ≥90	60≤eGFR<90	45≤eGFR<60	eGFR <45	
eGFR$_{MDRD}$					
Participants who died					
GFR ≥90	25	87*	0	0	112
60≤GFR<90	1**	567	0	0	568
45≤GFR<60	0	41**	91	0	132
GFR <45	0	0	5**	34	39
Total	26	695	96	34	851
Participants who did not die					
GFR ≥90	1,741	2,596**	0	0	4,337
60≤GFR<90	737*	15,823	0	0	16,560
45≤GFR<60	0	1,493*	1,086	0	2,579
GFR <45	0	0	77*	156	233
Total	2,478	19,912	1,163	156	23,709
Participants who developed AMI					
GFR ≥90	1	4*	0	0	5
60≤GFR<90	0**	48	0	0	48
45≤GFR<60	0	10**	14	0	24
GFR <45	0	0	0**	1	1
Total	1	62	14	1	78
Participants who did not develop AMI					
GFR ≥90	1,765	2,679**	0	0	4,444
60≤GFR<90	738*	16,342	0	0	17,080
45≤GFR<60	0	1,524*	1,163	0	2,687
GFR <45	0	0	82*	189	271
Total	2,503	20,545	1,245	189	24,482
Participants who developed stroke					
GFR ≥90	10	59*	0	0	69
60≤GFR<90	1**	427	0	0	428
45≤GFR<60	0	35**	59	0	94
GFR <45	0	0	2**	12	14
Total	11	521	61	12	605
Participants who did not develop stroke					
GFR ≥90	1,756	2,624**	0	0	4,380
60≤GFR<90	737*	15,963	0	0	16,700
45≤GFR<60	0	1,499*	1,118	0	2,617
GFR <45	0	0	80*	178	258
Total	2,493	20,086	1,198	178	23,955

*Improved reclassification; **worse reclassification using the CKD-EPI equation instead of the MDRD equation. Units of GFR, $ml \cdot min^{-1} \cdot 1.73 m^{-2}$.
Abbreviations as in Table 1.

and crude mortality was observed for the eGFR$_{CKDEPI}$ model, while that for eGFR and crude mortality in the GFR$_{MDRD}$ model was more of a gradual slope.

The relationship between CKD stage and death risk was U-shaped in the sex- and age-adjusted models and multivariate-adjusted models, and the lowest mortality rate was observed in stage 2 ($60–89 ml \cdot min^{-1} \cdot 1.73 m^{-2}$) for both the eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ models. The adjusted mortality rate in stage 3a was almost identical to that in stage 2 for the eGFR$_{MDRD}$ model, while a slightly higher mortality rate in stage 3a than in stage 2 was observed for the eGFR$_{CKDEPI}$ model. Adjusted mortality rate was significantly higher in stage 1 than in stage 2 for the eGFR$_{CKDEPI}$ model, while it was not significantly higher in the eGFR$_{MDRD}$ model. Adjusted incidence rates of AMI and stroke were similar between the 2 models for each stage.

Table 4 lists relative risks for death, AMI and stroke according to CKD stage for both the eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ models. Also listed are the results of model assessment using post-estimation analysis. A typical U-shaped relationship between mortality risk and CKD stage was observed for eGFR$_{CKDEPI}$, and a J-shaped relationship between mortality risk and CKD stage was observed for eGFR$_{MDRD}$. Two-fold higher risk for death was observed in stage 1 and stage 3b+ (eGFR $<45 ml \cdot min^{-1} \cdot 1.73 m^{-2}$) in the eGFR$_{CKDEPI}$ model, while mildly elevated risk for death was observed in stage 1 in the eGFR$_{MDRD}$ model. Risks for AMI and stroke were similar in each stage regardless of eGFR type. Although AUROC indicated that eGFR$_{CKDEPI}$ accurately discriminated subjects into persons with events or not, all model parameters (AIC,

BIC and Harrell's C) were almost identical between the eGFRCKDEPI and eGFRMDRD models. This suggests that no superiority existed in prediction of events either in the eGFRCKDEPI model or the eGFRMDRD model on multivariate-adjusted Cox regression analysis.

Table 5 lists detailed cross-tabulated classifications (CKD stage based on eGFRCKDEPI and on eGFRMDRD) for calculating NRI separately by endpoint. For predicting all-cause death, NRI was estimated to be 6.7% and Z statistic was estimated to be 4.78 (P<0.001). The eGFRCKDEPI model reclassified risk categories better than the eGFRMDRD model. For predicting incident AMI, NRI was –9.1% and Z statistic was estimated to be –1.89 (P=0.029). Use of eGFRCKDEPI made reclassification worse than using eGFRMDRD. For predicting incident stroke, NRI was –0.3% and Z statistic was estimated to be –0.20 (P=0.421) and no improvement was observed by using eGFRCKDEPI instead of eGFRMDRD.

Discussion

We compared risk predictabilities of mortality and cardiovascular morbidity between 2 models using GFR based on eGFRCKDEPI and that based on eGFRMDRD. In univariate analysis, discriminating ability using eGFRCKDEPI was significantly higher than that using eGFRMDRD to predict future death, AMI and stroke events (**Figure 3**; P<0.01). To compare discrimination abilities of the 2 models using eGFRCKDEPI and eGFRMDRD in multivariate-adjusted analysis, we compared model parameters including Harrell's C, AIC and BIC between the Cox regression model for CKD stage based on eGFRCKDEPI and that based on eGFRMDRD. We could not identify better discriminating ability in the eGFRCKDEPI model than that in the eGFRMDRD model. NRI analysis indicated that the CKD-EPI equation was associated with a significantly positive NRI for predicting all-cause death, while it was not associated with a positive NRI for predicting AMI or stroke.

To capture discrimination, AUROC is the most common popular metric.[13] A larger AUROC indicates a more appropriate predictor for separating subjects into a diseased group and non-diseased group.[13] Harrell et al extended the concept of discrimination from the logistic regression setting to survival analysis and developed concordance C statistics.[14] To quantitatively estimate fitness of the model, information-theoretic methods, such as AIC and BIC, have been developed.[29,30] Lower AIC and BIC indicate more appropriate goodness of fit for predicting the endpoint in a multivariate-adjusted model. The c statistic (AUROC and Harrell's C, etc), however, may not be optimal in assessing models that predict future risk or stratify individuals into risk categories.[18]

The question of whether novel risk factors can contribute to overall risk prediction independent of traditional risk factors and the question of whether a new model can more accurately stratify individuals into higher or lower risk categories of clinical importance have been challenging us to developing new ways for assessing adequate model predictability.[15,16,18] Several studies have offered new methods of assessment of risk prediction regarding reclassification tables.[17–19] Pencina et al proposed a new method of statistical analysis named "the net reclassification improvement" (NRI).[20] Assessment of NRI enables determination of new risk factors that contribute to improvement of risk prediction. Although we failed to show superiority of the eGFRCKDEPI model in discrimination ability, we managed to identify statistically significantly better performance of the eGFRCKDEPI model compared to the eGFRMDRD model on NRI analysis.

Superiority in discriminating ability in the eGFRCKDEPI model disappeared after multivariate adjustment and we found similar predictability in the 2 models. Several confounding factors may attenuate superiority in predictive ability in the eGFRCKDEPI model. Poisson regression analysis showed that age adjustment drastically converted a positive and steep linear relationship between mortality and CKD stage into a U-shaped relationship in the eGFRCKDEPI model. We also showed that age distribution was different for corresponding CKD stage between the 2 models in the baseline characteristics on cross-sectional analysis. The age-adjusted model suggested that the contribution of age to prediction of death was greater in the eGFRCKDEPI model, and the difference in predictive ability between the 2 models was attenuated after age adjustment. Moreover, age adjustment made the risk for death higher in CKD stage 1, especially in the eGFRCKDEPI model.

All-cause mortality and cardiovascular morbidity rates were high in subjects with normal eGFR (eGFR ≥90 ml·min^{-1}·1.73 m^{-2}) compared to subjects in stage 2 (60–89 ml·min^{-1}·1.73 m^{-2}) in the present study. Although most previous studies identified a linear relationship between cardiovascular morbidity and mortality risk and CKD stage, recent studies have shown that there is a U-shaped relationship between death risk and CKD stage based on eGFR.[12,33–36] The ARIC study found elevated risk for death and cardiovascular disease in subjects with elevated eGFR. Risk elevation started at eGFR=120 ml·min^{-1}·1.73 m^{-2}, and the lowest risk for death was observed for eGFR 90–119 ml·min^{-1}·1.73 m^{-2}.[12] Tonelli et al reported that risk elevation started at eGFR=75 ml·min^{-1}·1.73 m^{-2} and that the lowest risk for death was observed for eGFR 60–74 ml·min^{-1}·1.73 m^{-2}.[33] Although reduced GFR has been shown to contribute to higher risks for all-cause death and cardiovascular mortality and morbidity in previous studies, whether elevated GFR contributes to high risks for all-cause death and cardiovascular mortality and morbidity has not been elucidated.

Serum creatinine level is affected not only by GFR but also by other factors such as muscle metabolism. Persons with muscle wasting secondary to an illness such as malignancy, malnutrition or inflammatory disease and other deconditioning situations have a low serum creatinine level with apparently overestimated eGFR. They possibly have high risks for all-cause death and cardiovascular morbidity and mortality. The association between high eGFR and poor prognosis might be attributable to overestimation of eGFR due to low serum creatinine level in persons with muscle wasting.

Aside from the possible contribution of difference in muscle mass to eGFR, increased GFR might have contributed to elevated risks for death and cardiovascular morbidity and mortality. Hostetter et al reported that reduced mass of nephrons by artificial ablation yielded a marked increase in GFR and contributed to structural hypertrophy in an animal study.[37] This suggested that early-stage kidney failure was accompanied by hyperfiltration. A cross-sectional study showed that higher eGFR correlated with presence of hyperfiltration among diabetic patients with microalbumimnuria,[38] and hyperfiltration status observed in diabetic children was thought to be associated with subsequent development of kidney dysfunction expressed as microalbuminuria.[39]

Whether higher eGFR is associated with early-stage renal failure in non-diabetic subjects has not been fully elucidated and whether higher eGFR is associated with elevated risks for cardiovascular morbidity and mortality has also not been elucidated until now. We have shown only that higher GFR based on eGFRCKDEPI was associated with higher risk for all-cause death in a general population. Whether the association be-

tween higher eGFR and an elevated risk for death reflects the true relationship between elevated actual measured GFR and an elevated risk for death due to cardiovascular disease should be examined.

Several limitations to the present study should be noted. We could not measure GFR directly, and we therefore compared risk predictability of CKD stage based on estimation using $eGFR_{CKDEPI}$ and estimation using $eGFR_{MDRD}$. Participants <40 years of age accounted for only 3.4% of the total subjects, and the number of persons diagnosed in K/DOQI CKD stage 1 category (GFR $\geq 90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) was only 747 (8.9% of the total subjects). Subject age was biased to middle-aged to elderly, and most of these participants had mildly reduced kidney function (K/DOQI CKD stage 2), therefore this might have contributed to uncertainty in risk predictability in persons in K/DOQI CKD stage 1. The subject group consisted of persons who underwent annual health check-ups and were in relatively good condition, and we could not perform accurate examination in persons who were diagnosed as having K/DOQI CKD stage 4+ because of the small sample size. The considerably low incidence rate of AMI in this cohort study, which was also observed in a previous study in Japan,[40] also contributed to uncertainty in risk predictability for AMI.

In conclusion, better discrimination was obtained using the $eGFR_{CKDEPI}$ model than the $eGFR_{MDRD}$ model in univariate analysis. NRI analysis indicated that the use of $eGFR_{CKDEPI}$ instead of $eGFR_{MDRD}$ offered a statistically significant improvement in prediction of death. The use of the new equation for eGFR instead of the old equation may contribute to accurate risk assessment.

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Disclosures

Conflict of Interest: None declared.

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Supplementary Files

Supplementary File 1

Figure S1. The study area.

Table S1. Formulas for Calculating eGFR Based on CKD-EPI Equation and MDRD Equation

Table S2. Cross-Tables of CKD Stage Based on eGFRCKDEPI and eGFRMDRD

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ORIGINAL ARTICLE

Association between dietary behavior and risk of hypertension among Japanese male workers

Mitsumasa Umesawa[1,2], Akihiko Kitamura[2], Masahiko Kiyama[2], Takeo Okada[2], Yuji Shimizu[2,3], Hironori Imano[3], Tetsuya Ohira[3], Masakazu Nakamura[2], Koutatsu Maruyama[4] and Hiroyasu Iso[3], CIRCS Investigators

Dietary behavior can worsen or prevent hypertension. However, data on the association between dietary behavior and the risk of hypertension in Asians are limited. The aim of this study was to determine these associations in Japanese male workers. We conducted a prospective study of 30–71-year-old Japanese male workers in Osaka, Japan, between 2001 and 2011. The study subjects were 3486 normotensive males who were assessed for an average of 4.6 years using an annual survey. We defined hypertension by a systolic blood pressure of ⩾140 mm Hg, a diastolic blood pressure of ⩾90 mm Hg and/or the use of antihypertensive medications. Dietary behavior questionnaires were included in the annual surveys. For each question on dietary behavior, we calculated the odds ratios (ORs) for the risk of hypertension using logistic regression models. We used subjects who consistently gave affirmative answers in the baseline and end-point surveys as a reference. The number of new cases of hypertension was 846 among 3486 subjects. Compared with subjects who eat meat frequently, subjects who did not eat meat frequently showed a higher risk of hypertension (OR = 1.26, 95% confidence interval (CI): 1.00–1.59). Subjects who did not consume dairy products every day showed a higher risk of hypertension (OR = 1.39, 95% CI: 1.13–1.71) compared with those who did. Meat and dairy product intake was associated with the prevention of hypertension among Japanese male workers.
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Keywords: dietary behavior; epidemiology; prospective study

INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular disease in the Japanese, as well as in Western populations.[1–4] Therefore, it is important to determine the risk factors associated with hypertension in order to prevent hypertension and decrease the burden of cardiovascular disease. Although pharmacological treatment of hypertension is widely available, primary prevention of hypertension is desirable.

Several studies have reported that lifestyle is significantly associated with blood pressure[5] and the incidence of hypertension.[6] Dietary behavior seems to be an important risk factor because it is directly associated with energy intake, which in turn correlates with body weight control and nutrient intake and is associated with maintenance of the organism.

Several studies have examined dietary behavior in relation to the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet.[5–10] Both prospective studies[6–9] and intervention studies[5,10] found an inverse association between the Mediterranean diet or the DASH diet and the risk of hypertension or blood pressure levels. The Mediterranean diet involves an abundant intake of plant foods, adequate intake of dairy products and fish, and low intake of meats. The DASH diet involves an abundant or adequate intake of plant foods, fish and low-fat dairy products, with limited intake of sugar-sweetened foods, red meat and added fats.

For the Asian populations, only limited data are available on the association of dietary behavior and the risk of hypertension or blood pressure level. A cross-sectional study of the Chinese population showed an inverse association between fruit and milk intake and the prevalence of hypertension.[11] Another cross-sectional study of the Japanese population showed an inverse association between high fruit and vegetable intake and self-measured blood pressure levels.[12] To our knowledge, however, there are no published prospective studies that have examined the association of dietary behavior and the risk of hypertension or blood pressure levels in an Asian population. Of course, knowledge from Western countries is beneficial to some extent for Asians. The Japanese Society of Hypertension reviewed clinical and epidemiological studies published from around the world and released the Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2009.[13] In these guidelines, desirable dietary behavior was suggested; however, these guidelines were mainly

[1]Center for Medical Sciences, Ibaraki Prefectural University of Health Sciences, Ibaraki, Japan; [2]Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka, Japan; [3]Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Japan and [4]Department of Basic Medical Research and Education, Ehime University Graduate School of Medicine, Toon, Japan
Correspondence: Dr M Umesawa, Center for Medical Sciences, Ibaraki Prefectural University of Health Sciences, Ami 4669-2, Inashiki-gun, Ibaraki 300-0394, Japan.
E-mail: starlight-shower@nifty.com
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based on the DASH diet. We believe that more data are needed for Asians because an Asian diet is different from that of Western countries.

Our *a priori* hypothesis was that the development of hypertension is associated with dietary behavior in the Japanese population. Dietary behaviors that lead to obesity or involve high sodium intake may increase the risk of hypertension, whereas dietary behaviors that include the consumption of fruits, vegetables and dairy products may reduce the risk of hypertension. To test our hypothesis, we performed the present prospective study in Japanese male workers.

METHODS

Study subjects

The participants were 30–71-year-old (mean age: 45.0 years) male workers who were employees of six companies in the Osaka area of central Japan and underwent serial government-sponsored annual health checkups. The total number of participants was 6554 at the beginning of the study. We excluded 1743 participants because they were diagnosed with hypertension ($\geqslant$140 mm Hg systolic blood pressure and/or $\geqslant$90 mm Hg diastolic blood pressure and/or those who were taking antihypertensive medications) on the baseline cardiovascular disease risk survey. During the follow-up, 1142 participants (mean age: 46.8 years) dropped out of the study following a failure to complete a health checkup. Furthermore, we excluded 183 participants because their serum creatinine concentrations were not measured. Thus, data on 3486 subjects (mean age: 42.9 years) were used for this analysis. We obtained informed consent from all subjects according to the ethical guidelines for epidemiological research by the Ministry of Health, Labor and Welfare. The study was approved by the Ethics Committee of Osaka Medical Center for Health Science and Promotion.

Risk factor survey

The annual Cardiovascular Disease Risk Surveys were performed from 2001 to 2011. The arterial systolic blood pressures and fifth-phase diastolic blood pressures were measured by well-trained observers using a standard mercury sphygmomanometer on the right arm during the survey. The participants were seated quietly for at least 5 min before the measurement. We used the data from the first measurement because the blood pressure was not measured twice in all subjects. Individuals with hypertension included those found to have high blood pressure ($\geqslant$140 mm Hg systolic blood pressure and/or $\geqslant$90 mm Hg diastolic blood pressure), as well as those being treated with antihypertensive medications.

With regard to potential confounders, the body mass index was calculated by dividing the weight in kilograms by the height in meters squared. The height was measured with subjects wearing socks, and the weight was measured with subjects wearing light clothing. Every participant was interviewed to determine their usual weekly alcohol consumption in *go* units, a traditional Japanese unit of volume equivalent to 23 grams of ethanol. We divided weekly ethanol intake by seven to calculate the average daily alcohol intake. The smoking habits and history of the subjects were also determined during the interview, as well as the history of hypertension, stroke, coronary heart disease, renal disease and the use of antihypertensive medications. The estimated glomerular filtration rate was calculated using the following formula established by the working group of the Japanese Chronic Kidney Disease Initiative: estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2}) = 1.94 $\times$ (serum creatinine)$^{-1.094}$ $\times$ (age)$^{-0.287}$.[14] Since 2001, serum creatinine has been measured using the enzymatic method.

Dietary behavior survey

The dietary behavior survey was carried out as part of the annual Cardiovascular Disease Risk Survey from 2001 to 2011 using questionnaires. The questionnaires were based on a health assessment in Japanese.[15] Well-trained public health nurses helped participants who had difficulty in answering the questionnaires. The survey consisted of 19 items related to dietary behavior (Table 1). Subjects answered either 'yes' or 'no.' We examined the reproducibility of the questionnaire by using data from 2251 male subjects who were free from hypertension, hypercholesterolemia and diabetes at baseline and received a dietary behavior survey again the next year. The range of the concordance rate of each question was from 73.1 (dietary behavior concerned with meat intake) to 89.2% (dietary behavior concerned with breakfast intake).

Table 1 19 questions of dietary behavior survey

1. Do you have breakfast?
2. Do you have a meal just before bedtime?
3. Do you eat until you are full?
4. Do you eat between meals or before bedtime every day?
5. Do you consume soft drinks every day?
6. Do you have fried food every day?
7. Do you have one or more eggs every day?
8. Do you have meat frequently?
9. Do you have fish or shellfish more than twice a week?
10. Do you season all food salty?
11. Do you have salty soup less than twice a day?
12. Do you have all-noodle soup?
13. Do you have food preserved in salt less than three times a week?
14. Do you use salty sauce before checking the taste?
15. Do you have salty pickles less than twice a day?
16. Do you have vegetables or seaweed at every meal?
17. Do you have fruits every day?
18. Do you have soy products every day?
19. Do you consume dairy products every day?

Statistical analysis

The follow-up period was calculated from the day of the first cardiovascular risk survey (baseline survey) to the day of the end-point survey. For subjects who were diagnosed with hypertension, we defined the end-point survey as the survey in which the subject was first diagnosed with hypertension. For subjects who were consistently diagnosed as normotensive, we defined the end-point survey as the last survey.

We prepared 19 dietary behaviors and divided the subjects into four groups according to the answers provided in the baseline and end-point questionnaires. Subjects who answered 'yes' in both the baseline and end-point questionnaires were assigned to group 1. Subjects who answered 'yes' in the baseline questionnaire and 'no' in the end-point questionnaire were assigned to group 2. Subjects who answered 'no' in the baseline questionnaire and 'yes' in the end-point questionnaire were placed in group 3, and subjects who answered 'no' in both the baseline and end-point questionnaires were placed in group 4 on the questions 1, 3, 4–9, 11, 13 and 15–19. As for questions 2, 10, 12 and 14, the subjects were placed in the four groups based on answers opposite to the rules showing above.

Age-adjusted and multivariate-adjusted means and the magnitude of confounding variables were calculated and tested using an analysis of covariance. We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) by using the logistic regression model for age-adjusted ORs and multivariate-adjusted ORs for the development of hypertension. We used group 1 as the reference group. We used the baseline age, job, body mass index, daily alcohol intake, smoking habits, estimated glomerular filtration rate and systolic blood pressure level at the baseline survey as the confounding variables.

Although there were 19 items in the questionnaire, we listed the results of only 5 items in the tables for better presentation. The results of the other 14 items are listed in Supplementary Table 1.

Furthermore, we examined the differences in the baseline characteristics of 3486 subjects who followed up and 1142 subjects who did not follow-up. The results are reported in Supplementary Table 2.

We used the SAS version 9.1.3 software (SAS Institute Inc., Cary, NC, USA) for all analyses. *P*-values <0.05 were considered statistically significant (on two-tailed analyses).

RESULTS

During an average 4.6-year follow-up for the 3486 subjects, 846 incident cases (24.3%) of hypertension were documented. Table 2 lists the characteristics of the subjects in the first cardiovascular survey according to the five dietary behaviors that were significantly associated with the risk of hypertension. Subjects who consistently did not have one or more egg every day at both the baseline and end-point surveys (group 4) had a higher diastolic blood pressure

Table 2 Baseline characteristics of subjects according to the answers given to the questionnaires of the baseline and end-point surveys

	Answers to questionnaires (baseline/end point)				
	Yes/Yes (group 1)	*Yes/No (group 2)*	*No/Yes (group 3)*	*No/No (group 4)*	*Lack of answers*
Subjects who had one or more eggs every day					
Number and percentage of subjects	800 (23%)	539 (15%)	406 (12%)	1740 (50%)	1 (0%)
Age (years)	41.7	42.0	42.1	44.0	55.0
Body mass index ($kg\,m^{-2}$)[a]	23.6	23.5	23.3	23.1**	27.3
Alcohol intake (g ethanol per day)[a]	25.6	23.7	20.7**	19.4**	40.2
Current smokers (%)[a]	47	49	42	47	0
Systolic blood pressure (mm Hg)[b]	116.7	116.9	116.5	116.5	116.7
Diastolic blood pressure (mm Hg)[b]	73.0	73.4	72.8	73.8*	78.0
Estimated glomerular filtration rate ($ml\,min^{-1}\,1.73\,m^{-2}$)[b]	82.5	83.3	82.0	81.4*	87.4
Subjects who had meat frequently					
Number and percentage of subjects	872 (25%)	518 (15%)	485 (14%)	1606 (46%)	5 (0%)
Age (years)	39.5	42.2	41.9	45.3	52.0
Body mass index ($kg\,m^{-2}$)[a]	23.5	23.5	23.4	23.0**	25.5
Alcohol intake (g ethanol per day)[a]	23.1	23.5	20.8	20.6*	12.2
Current smokers (%)[a]	47	51	42	46	19
Systolic blood pressure (mm Hg)[b]	116.8	116.7	116.7	116.4	108.6
Diastolic blood pressure (mm Hg)[b]	73.5	74.0	73.2	73.4	71.7
Estimated glomerular filtration rate ($ml\,min^{-1}\,1.73\,m^{-2}$)[b]	82.0	81.9	81.7	82.3	83.1
Subjects who did not have all-noodle soup					
Number and percentage of subjects	1945 (56%)	235 (7%)	444 (13%)	861 (25%)	1 (0%)
Age (years)	43.2	42.9	42.8	42.4	35.0
Body mass index ($kg\,m^{-2}$)[a]	23.0	23.0	23.7**	23.7**	27.3
Alcohol intake (g ethanol per day)[a]	19.7	24.0*	23.5**	24.5**	40.4
Current smokers (%)[a]	44	45	47	52**	100
Systolic blood pressure (mm Hg)[b]	116.6	117.0	117.1	116.1	126.8
Diastolic blood pressure (mm Hg)[b]	73.5	73.4	73.6	73.3	80.2
Estimated glomerular filtration rate ($ml\,min^{-1}\,1.73\,m^{-2}$)[b]	81.9	83.1	81.6	82.3	89.1
Subjects who consumed dairy products every day					
Number and percentage of subjects	1214 (35%)	443 (13%)	419 (12%)	1408 (40%)	2 (%)
Age (years)	43.6	41.8	44.0	42.4	51.0
Body mass index ($kg\,m^{-2}$)[a]	23.4	23.2	23.2	23.2*	26.9
Alcohol intake (g ethanol per day)[a]	18.5	20.0	20.9	25.1**	27.3
Current smokers (%)[a]	36	38	48**	58**	49
Systolic blood pressure (mm Hg)[b]	116.4	117.0	116.8	116.6	123.1
Diastolic blood pressure (mm Hg)[b]	73.1	73.6	73.1	73.8*	80.1
Estimated glomerular filtration rate ($ml\,min^{-1}\,1.73\,m^{-2}$)[b]	81.5	81.6	80.9	83.0**	83.1
Subjects who ate between meals or before bedtime every day					
Number and percentage of subjects	297 (9%)	237 (7%)	285 (8%)	2663 (76%)	4 (0%)
Age (years)	41.8	40.6	42.6	43.3	48.5
Body mass index ($kg\,m^{-2}$)[a]	23.4	23.7	22.9*	23.2	25.3
Alcohol intake (g ethanol per day)[a]	12.9	16.9	13.9	23.9**	17.6
Current smokers (%)[a]	34	46**	44*	48**	25
Systolic blood pressure (mm Hg)[b]	115.7	116.5	115.9	116.8	128.8*
Diastolic blood pressure (mm Hg)[b]	72.7	72.9	72.2	73.7*	80.0
Estimated glomerular filtration rate ($ml\,min^{-1}\,1.73\,m^{-2}$)[b]	81.4	82.9	83.4	81.9	87.6

*$P<0.05$ and **$P<0.01$.
[a]Adjusted for age (years).
[b]Adjusted for age (years), body mass index ($kg\,m^{-2}$), ethanol intake (g per day) and current smoking (yes or no).

compared with subjects who consistently did (group 1, $P=0.03$). Subjects who did not consistently consume dairy products every day (group 4) had a higher diastolic blood pressure compared with subjects who consistently did (group 1, $P=0.03$). Subjects who did not consistently eat between meals or before bedtime every day (group 4) had a higher systolic blood pressure compared with subjects who consistently did (group 1, $P=0.04$).

Table 3 shows the age-adjusted and multivariate-adjusted ORs of the risk of hypertension according to the above five dietary behaviors that showed statistical significance. After adjusting for the confounding variables, the OR values were significantly higher in subjects who consistently did not eat meat frequently (group 4) than subjects who consistently did eat meat frequently (group 1) (OR = 1.32, 95% CI: 1.05–1.65; $P=0.02$). Regarding dairy products, the OR values were higher in subjects who consistently did not consume dairy products every day (group 4) and who changed their dietary behavior from consuming dairy products every day to not (group 2) than those who consistently did consume dairy products (group 1) (OR = 1.37, 95% CI: 1.11–1.68; $P=0.003$ and OR = 1.43, 95% CI: 1.08–1.89; $P=0.01$, respectively). The OR values were higher in subjects who consistently did not eat between meals or before bedtime every day (group 4) than those who consistently did (group 1) (OR = 1.41, 95% CI: 1.00–1.98; $P=0.05$). The OR values were higher in subjects who changed their dietary behaviors from eating one or more eggs every day to not eating eggs (group 2) than those who did consistently eat one or more eggs every day (group 1) (OR = 1.37, 95% CI: 1.04–1.80; $P=0.02$). The OR values were higher in subjects who changed their dietary behavior from consuming noodle soup to not consuming noddle soup (group 3) than those who did not consistently consume noodle soup (group 1) (OR = 1.32, 95% CI: 1.03–1.70; $P=0.03$).

Table 4 shows the multivariate-adjusted ORs and 95% CIs for the risk of hypertension after further adjustment for each dietary behavior listed in Table 2. The associations between dietary behaviors and the risk of hypertension did not change significantly, but the association with eating between meals or before bedtime was no longer statistically significant ($P=0.09$).

We also calculated the age-adjusted and multivariate-adjusted ORs of the risk of hypertension according to the dietary behaviors that did not show statistical significance. Dietary behaviors characterized by not eating breakfast, eating a meal just before bedtime, not eating fried food, adding salt to meals, using a salty sauce before checking the taste, not having vegetables or seaweed at every meal and not eating fruits led to a higher risk of hypertension, whereas dietary

Table 3 Age-adjusted and multivariate-adjusted ORs of the development of hypertension according to the answers given to the questionnaires in the baseline and end-point surveys

	Answers to questionnaires (baseline/end point)			
	Yes/Yes (group 1)	*Yes/No (group 2)*	*No/Yes (group 3)*	*No/No (group 4)*
Subjects who had one or more eggs every day				
Number of subjects	6	539	406	1740
Development of hypertension (%)	24	28	22	24
Age-adjusted OR and 95% CI	1.00	1.22 (0.95–1.57)	0.90 (0.68–1.20)	0.91 (0.75–1.11)
Multivariate-adjusted OR and 95% CI	1.00	1.37 (1.04–1.80)	1.08 (0.79–1.48)	1.19 (0.95–1.48)
Subjects who had meat frequently				
Number of subjects	872	518	485	1606
Development of hypertension (%)	21	23	23	27
Age-adjusted OR and 95% CI	1.00	1.02 (0.79–1.33)	1.01 (0.78–1.33)	1.15 (0.94–1.41)
Multivariate-adjusted OR and 95% CI	1.00	1.02 (0.77–1.36)	1.05 (0.78–1.41)	1.32 (1.05–1.65)
Subjects who did not have all-noodle soup				
Number of subjects	1945	235	444	861
Development of hypertension (%)	23	21	32	24
Age-adjusted OR and 95% CI	1.00	0.90 (0.65–1.26)	1.57 (1.25–1.97)	1.05 (0.87–1.27)
Multivariate-adjusted OR and 95% CI	1.00	0.83 (0.58–1.19)	1.32 (1.03–1.70)	0.94 (0.76–1.16)
Subjects who consumed dairy products every day				
Number of subjects	1214	443	419	1408
Development of hypertension (%)	21	26	25	26
Age-adjusted OR and 95% CI	1.00	1.44 (1.12–1.86)	1.24 (0.95–1.61)	1.41 (1.18–1.70)
Multivariate-adjusted OR and 95% CI	1.00	1.42 (1.08–1.88)	1.16 (0.87–1.55)	1.36 (1.11–1.67)
Subjects who ate between meals or before bedtime every day				
Number of subjects	297	237	284	2658
Development of hypertension (%)	18	20	21	26
Age-adjusted OR and 95% CI	1.00	1.24 (0.80–1.92)	1.26 (0.83–1.90)	1.57 (1.15–2.14)
Multivariate-adjusted OR and 95% CI	1.00	1.11 (0.69–1.78)	1.38 (0.88–2.17)	1.41 (1.00–1.98)

Abbreviations: CI, confidence interval; OR, odds ratio.
Adjusted for age (years), job, body mass index ($kg\,m^{-2}$), ethanol intake (g per day), current smoking (yes or no), estimated glomerular filtration rate ($ml\,min^{-1}\,1.73\,m^{-2}$) and systolic blood pressure level from baseline survey (mm Hg).

Table 4 Multivariate-adjusted odds ratios of the development of hypertension after further adjustment for dietary patterns

	Answers to questionnaires (baseline/end point)			
	Yes/Yes (group 1)	*Yes/No (group 2)*	*No/Yes (group 3)*	*No/No (group 4)*
Subjects who had one or more eggs every day				
OR and 95% CI	1.00	1.33 (1.00–1.75)	1.07 (0.78–1.46)	1.11 (0.89–1.40)
Subjects who had meat frequently				
OR and 95% CI	1.00	0.98 (0.73–1.31)	0.99 (0.74–1.34)	1.26 (1.00–1.59)
Subjects who did not have all-noodle soup				
OR and 95% CI	1.00	0.83 (0.58–1.19)	1.32 (1.02–1.71)	0.95 (0.77–1.18)
Subjects who consumed dairy products every day				
OR and 95% CI	1.00	1.43 (1.07–1.89)	1.16 (0.87–1.55)	1.39 (1.13–1.71)
Subjects who ate between meals or before bedtime every day				
OR and 95% CI	1.00	1.07 (0.66–1.72)	1.37 (0.87–2.16)	1.35 (0.96–1.90)

Abbreviations: CI, confidence interval; OR, odds ratio.
Adjusted for age (years), job, body mass index ($kg\,m^{-2}$), ethanol intake (g per day), current smoking (yes or no), estimated glomerular filtration rate ($ml\,min^{-1}\,1.73\,m^{-2}$), systolic blood pressure level from baseline survey (mm Hg) and other dietary behaviors.

behaviors characterized by consuming salty soup, eating foods preserved in salt, eating salty pickles and avoiding soy products led to a lower risk of hypertension. Dietary behaviors characterized by eating until full, consuming soft drinks and having fish or shellfish were not significantly associated with hypertension.

DISCUSSION

The main finding of our study of Japanese male workers was that the dietary behavior of eating meat and the daily intake of dairy products were inversely associated with the development of hypertension, even after adjusting for other dietary behaviors. Refraining from eating one or more eggs or having noodle soup was positively associated with the development of hypertension.

To our knowledge, no epidemiological study has reported a significant association between meat intake and the risk of hypertension. The Mediterranean diet and the DASH diet recommend a lower intake of red meat to prevent hypertension.[5–10] However, in the present study, subjects who did not eat meat frequently demonstrated a 29% higher risk of hypertension compared with subjects who had meat frequently.

As for dairy product intake, several European and US epidemiological studies reported the association between dairy product intake and the risk of hypertension.[16–18] Among middle-aged and elderly females in the United States, the highest and median quintiles of dairy product intake (2.99–22.1 and 1.40–1.92 servings per day, respectively) showed a 14% and 7% lower risk of hypertension, respectively, compared with the lowest quintile (0–0.85 servings per day).[16] Among young overweight US adults, the lowest category of dairy product intake (0–9 times per week) showed a three-fold higher incidence of hypertension compared with the top category of dairy product intake (>35 times per week).[17] Among Dutch males and females aged >55 years, the highest quartile of dairy product intake (median: 691 g per day) showed a 24% lower incidence of hypertension compared with the lowest quartile (164 g per day).[18] In the present study, subjects who did not consume dairy products every day at the baseline and end-point surveys had a 36% higher risk of hypertension, and those who stopped consuming dairy products every day between the baseline and end-point surveys had a 44% higher risk of hypertension compared with the subjects who consumed dairy products every day at baseline and end-point surveys. This result implies that the regular intake of dairy products seems to prevent hypertension. Our study is the first to show the association between dairy products and the development of hypertension in an Asian population.

The mechanism of the inverse association of meat and dairy product intake with hypertension merits some discussion. Specific amino acids that are rich in animal products, such as arginine, taurine, tryptophan and tyrosine, are involved in the control of the vascular system. For example, L-arginine is a vasodilator and substrate of nitric oxide. In a human experiment, an infusion of L-arginine produced an immediate reduction in the blood pressure.[19] Taurine seems to affect the central nervous system. In an animal experiment, taurine infusion into the brain ventricles lowered blood pressure,[20] and a human experiment demonstrated that supplemental intake of taurine at 6 g per day for 7 days lowered blood pressure levels.[21] Tryptophan and tyrosine also seem to affect the central nervous system by enhancing the synthesis of serotonin, as demonstrated in animal experiments;[22,23] however, there is no evidence for a similar effect in humans. Although eggs and fish also contain these specific amino acids, they are frequently seasoned with salt in Japan. Therefore, dietary behaviors related to egg and fish intake did not show a significant inverse association with the risk of hypertension. As for dairy products, other mechanisms may exist. Milk peptides have antihypertensive activity by inhibiting angiotensin-1-converting enzyme.[24] Calcium and magnesium intake is inversely associated with blood pressure levels.[8,25]

With regard to noodle soup, which has a high sodium content, subjects who changed their dietary behavior from having noodle soup to avoiding noodle soup showed a higher risk of hypertension, although subjects who had an all-noodle soup diet did not consistently show a higher risk of hypertension. We suppose the reason was that subjects who developed high blood pressure levels among subjects who had an all-noodle soup diet at the baseline survey were careful to reduce sodium intake and stopped the all-noodle soup diet before the end-point survey.

Subjects who changed their dietary behavior from consuming one or more eggs every day to avoiding eggs showed a higher risk of hypertension, although subjects who did not consistently consume one or more eggs every day showed a statistically insignificant higher risk of hypertension. We suppose the reason was that subjects who stopped consuming eggs every day lowered their protein intake, which led to an increase in blood pressure. In a recent randomized trial of protein supplementation, in which egg protein formed 20% of the total protein intake, increased protein intake lowered blood pressure levels.[26]

Based on the results of the present study, Japanese people should consume meat and dairy products frequently to prevent hypertension. The recommendation of high meat intake is different from the DASH diet. However, a previous cross-sectional study of Japanese subjects showed an inverse association between animal protein intake and blood pressure levels,[27] which adds support to the notion that Japanese people should consume meat.

The strength of the present study is that the methodology was superior to that of previous cross-sectional studies of Japanese populations.[12,28] Prospective studies have little informational bias, and their results are more revealing than those of cross-sectional studies. The results of prospective studies also reinforce the causal relationships between risk factors and the development of hypertension more clearly than those of cross-sectional studies.

The limitations of the present study warrant discussion. First, we were unable to obtain the precise date of the development of hypertension because our analysis was based on information from annual cardiovascular risk checks. We then used logistic regression analysis to calculate the ORs based on information from the baseline questionnaire. Second, our questionnaire only allowed subjects to choose answers 'yes' or 'no,' which made it difficult to evaluate the dose–response association between each type of dietary behavior and the development of hypertension. Furthermore, we did not determine the validity of the questionnaire fully. Only questions concerning sodium intake were validated.[29,30] However, we previously compared our questionnaire with other validated food frequency questionnaires and found that the subjects who reported eating something frequently had higher intake than the other subjects,[31] which may add some support to the validity of the questionnaire. Third, we used the first blood pressure measurement in the present study due to the low number of subjects in whom blood pressure levels were measured twice. However, inclusion of the second measurement in the analysis, when available, did not change the results. In addition, we used systolic blood pressure levels measured at baseline in the multiple logistic regression analysis. We confirmed that the results did not change when we used diastolic instead of systolic blood pressure levels. Fourth, because of poor follow-up, we excluded from the analyses 1142 subjects who had a potentially higher risk of hypertension because of age, blood pressure levels and estimated glomerular filtration rate. Fifth, the present study included only males, and the results cannot be applied to females.

In conclusion, our prospective study of Japanese male workers showed that the intake of meat, dairy products and eggs was inversely associated with the risk of hypertension, whereas the intake of noodle soup was positively associated with the risk of hypertension. These results point to a beneficial dietary behavior that can prevent hypertension in male Japanese workers. Further epidemiological studies and clinical trials are necessary to establish the best dietary behavior for the prevention of hypertension among Japanese males.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Non-fasting blood glucose and risk of incident coronary heart disease in middle-aged general population: The Circulatory Risk in Communities Study (CIRCS)

Hironori Imano [a,b,*], Hiroyasu Iso [a], Masahiko Kiyama [b], Kazumasa Yamagishi [c], Tetsuya Ohira [a,b], Shinichi Sato [d], Hiroyuki Noda [a,b], Kenji Maeda [b], Takeo Okada [b], Takeshi Tanigawa [e], Akihiko Kitamura [b] and The CIRCS Investigators

[a] Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita 565-0871, Japan
[b] Osaka Medical Center for Health Science and Promotion, 1-3-2 Nakamichi, Higashinari-ku, Osaka 537-0025, Japan
[c] Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8575, Japan
[d] Division of Health Epidemiology, Chiba Prefectural Institute of Public Health, Nitona government office building, 666-2 Nitonacho, Chuo-ku, Chiba 260-8715, Japan
[e] Department of Environmental Health and Social Medicine, Ehime University Graduate School of Medicine, 454 Shitsukawa, Toon 791-0295, Japan

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ABSTRACT

Objective. The objective was to determine whether non-fasting glucose concentration is a predictor for incident coronary heart disease.

Methods. We investigated a cohort data of 9,900 40- to 69-year-old residents in four Japanese communities for 1975–1986 baseline surveys of the Circulatory Risk in Communities Study (CIRCS). Non-fasting blood glucose concentrations were available for 7,332 participants. Diabetic type was defined as a glucose level of ≥11.1 mmol/L and/or the use of medication for diabetes mellitus.

Results. A total of 170 coronary heart disease including 113 myocardial infarctions occurred in non-fasting participants within the median 22-year follow-up period. Multivariable hazard ratios (HRs) of incident coronary heart disease for the participants with diabetic type compared with the normal type were 1.98 (0.84–4.68) for men, 3.39 (1.47–7.81) for women, and 2.47 (1.37–4.46) for total subjects. Corresponding HRs for myocardial infarction were 2.14 (0.83–5.55), 5.70 (2.21–14.67) and 3.17 (1.65–6.10), respectively. Multivariable HRs of incident coronary heart disease per one standard deviation of serum glucose levels were 1.17 (1.02–1.36), 1.19 (1.03–1.38), and 1.19 (1.08–1.32), respectively. The corresponding HRs for myocardial infarction were 1.18 (1.00–1.38), 1.27 (1.07–1.49) and 1.23 (1.10–1.37).

Conclusion. Non-fasting glucose concentration, either as diagnosis of diabetic type or as continuous variable, proved to be an independent predictor for incident coronary heart disease in middle-aged general population.

Introduction

A recent meta-analysis of 102 prospective observational studies (Sarwar et al., 2010) found that diabetes mellitus and fasting glucose concentration were associated with increased risk of coronary heart disease and ischemic stroke. Further, a meta-analysis of five prospective randomized controlled trials demonstrated that the intensive glycemic control reduced risk of coronary heart disease (Ray et al., 2009).

On the other hand, previous prospective studies examined the association of the fixed-time postload or postprandial glucose levels with mortality from or incidence of cardiovascular disease. For example, the 1 h or 2 h postload glucose concentration in the oral glucose tolerance test (OGTT) was a good predictor for death or events associated with cardiovascular diseases among subjects of Americans (Lowe et al., 1997), Europeans (DECODE Study Group, 2001), Asians (Nakagami et al., 2004), Japanese ancestry in Hawaii (Donahue et al., 1987) and Japanese (Tominaga et al., 1999). The 1 h or 2 h postprandial glucose concentration was also a stronger predictor for cardiovascular events than fasting glucose concentration among patients with type 2 diabetes (Cavalot et al., 2006; Hanefeld et al., 1996). The importance of the management of postprandial or postload glucose was addressed in the guidelines by the European Society of Cardiology and the European Association for the Study of Diabetes (Rydén et al., 2007) and by the International Diabetes Federation (2007) to prevent cardiovascular disease.

However, the measurement of fix-time postload or postprandial glucose levels is practically difficult to be performed at health screening for general populations, and the data of non-fasting blood glucose are commonly obtained. It is uncertain whether non-fasting glucose

* Corresponding author at: Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka, 565-0871, Japan. Fax: +81 6 6879 3919.
E-mail address: imano@pbhel.med.osaka-u.ac.jp (H. Imano).

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concentration is a predictor for incident coronary heart disease. To confirm that non-fasting glucose concentration, either as diagnosis of diabetic type or as continuous variable, is a predictor for incident coronary heart disease, we explored the data of a community-based prospective study of middle aged men and women.

Methods

Study populations

The present analyses were conducted in the Circulatory Risk in Communities Study (CIRCS) (Imano et al., 2009, 2012; Ohira, 2010), which is a new generic name of the prior and ongoing epidemiological studies, such as Akita–Osaka Study, Ikawa Study and Kyowa Study since 1963. The study populations comprised 10,126 residents (4,092 men and 6,034 women) aged 40–69 years in four communities: Ikawa town (Kitamura et al., 2008; Shimamoto et al., 1989) (a rural community in Akita Prefecture in northwestern Japan), the Minami-Takayasu district (Kitamura et al., 2008) in Yao City (a southwestern suburb in Osaka Prefecture), Noichi town (Okamura, 1994) (a rural community in Kochi Prefecture in southwestern Japan); and Kyowa town (Iso et al., 1996) (a rural community in Ibaraki Prefecture in central Japan). The baseline surveys were conducted in 1975 to 80 in Ikawa town, in 1975 to 84 in the Minami-Takayasu district, in 1975 to 80 in Noichi town, and in 1981 to 86 in Kyowa town. The census population aged 40–69 years old was 2,291 in 1975 for Ikawa town, 5,538 in 1980 for the Minami-Takayasu district, 3,599 in 1975 for Noichi town, and 5,408 in 1980 for Kyowa town. The study participation rate was 60%. After exclusion of 226 participants with a history of coronary heart disease and/or stroke at baseline, the data for 7,332 (2,916 men and 4,416 women) non-fasting subjects were analyzed.

Informed consent was obtained for conducting this study, which was based on the guidelines of the Council for International Organizations of Medical Sciences (1991). This study was approved by the ethics committees of the Osaka Medical Center for Health Science and Promotion and of Osaka University.

Follow-up and ascertainment of cases

Follow-up lasted until the end of 2005 for Noichi and Kyowa, of 2008 for Minami-Takayasu, and of 2009 for Ikawa was terminated at the first incident of coronary heart disease or acute myocardial infarction, exit from the community or death.

The details of endpoint determination have been described in a previous CIRCS report (Kitamura et al., 2008; Shimamoto et al., 1989). To confirm the diagnosis, all living patients were telephoned, visited or invited to take part in risk factor surveys or a medical history was obtained from their families. In addition, medical records in the local clinics and hospitals were reviewed. In case of death, histories were obtained from families and/or attending physicians and medical records were reviewed.

The criteria for coronary heart disease were modified from those established by the World Health Organization Expert Committee (1962) and have been described in a previous CIRCS report (Imano et al., 2011; Kitamura et al., 2008). Definite myocardial infarction was diagnosed as typical severe chest pain (lasting at least 30 minutes) accompanied by the appearance of new abnormal and persistent Q or QS waves, consistent changes in cardiac enzyme levels, or both. Probable myocardial infarction was indicated by typical chest pain, but for which no electrocardiographic findings or findings related to enzyme activity were available. Myocardial infarction was considered present if either definite or probable myocardial infarction was diagnosed. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or by the use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 h of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by not more than 1 h of symptoms. Coronary heart disease was defined as including myocardial infarction, angina pectoris, and sudden cardiac death.

Baseline examination

Blood was drawn into a plain, siliconized glass tube and the serum was separated immediately after centrifugation. The time intervals since the last meal were 0 to <1 h (4.2%), 1 to <2 h (27.3%), 2 to <3 h (54.6%), 3 to <4 h (9.8%), and 4 to <8 h (4.0%). Serum glucose was measured with the cupric-neocuproine method using SMA-6/60 (Technicon, Tarrytown, NY) between 1975 and August 31st in 1986 and with the hexokinase method using SMAC (Technicon) from September 1st in 1986. Glucose values (mmol/L) obtained using the first method were adjusted with the formula: $0.0474\times$(glucose concentration in mg/dL) + 0.541. Glucose values were classified into three categories (diabetic type, prediabetic type and normal type). Diabetic type was defined as a glucose level of ≥11.1 mmol/L and/or the use of medication for diabetes mellitus. Normal type was defined as no use of medication for diabetes mellitus and a glucose level of <7.8 mmol/L. Borderline type was defined in those who belong neither to diabetic nor to normal types.

Serum total cholesterol was measured with the Liebermann–Burchard direct method using Autoanalyzer II (Technicon) for the period 1975–1979 and SMA-6/60 from 1979 to 1986. Serum triglycerides were measured with the fluorometric method using Autoanalyzer II from 1975 to 1986. For 60% of total sample ($n=4,385$), high-density lipoprotein (HDL) cholesterol was measured after heparin-manganese precipitation using the Libermann–Burchard method.

All measurements of serum glucose, serum total cholesterol, serum triglycerides and HDL-cholesterol were performed at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network. This laboratory has been standardized since 1975 by the Centers for Disease Control-National Heart Lung and Blood Institute (CDC-NHLBI) Lipid Standardized Program provided by the CDC (Atlanta, GA) and successfully met the criteria for both precision and accuracy of serum total cholesterol, triglycerides and HDL-cholesterol measurements (Nakamura et al., 2003).

Blood pressures were measured by trained physicians using standard mercury sphygmomanometers and standardized epidemiological methods (Imano et al., 2009). Height was measured with the subjects in stocking feet and their weight while wearing light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

An interview was conducted to ascertain smoking status, the number of cigarettes smoked per day, usual alcohol intake per week, menopause status, and the use of medication for diabetes mellitus or hypertension.

Statistical analyses

Analysis of covariance was used to test for differences in age-adjusted means and proportions of baseline characteristics according to serum glucose category. HRs and 95% confidence intervals (CIs) for incident myocardial infarction were calculated with the aid of Cox proportional hazards regression models. We tested the assumption of proportional hazards and found no violation of the proportionality principle.

We calculated the sex-specific and sex-adjusted HRs of each diabetic type and borderline type against the normal type as the referent, and the corresponding HRs per one standard deviation increment in serum glucose level (1.9 mmol/L). The initial model was adjusted only for age, while the multivariable adjustment included adjustments for age, sex (for total participants), community, sex-specific quartiles of body mass index (kg/m^2), of serum triglycerides (mmol/L), serum total cholesterol level (mmol/L), systolic blood pressure (mmHg), antihypertensive medication use, cigarette smoking status (never, former and current 1–24 or ≥25 cigarettes per day), alcohol intake (never, former, and current <46, 46–68 or ≥69 g ethanol per day), time category since last meal (0 to <1 h, 1 to <2 h, 2 to <3 h, 3 to <8 h) and for women, menopausal status. Further adjustment for HDL-cholesterol (mmol/L) was conducted among a subsample in which the data on HDL-cholesterol were available.

All statistical analyses were performed with the Statistical Analysis System (SAS) for Windows (version 9.3; SAS Inc, Cary, NC). All p-values for statistical tests were two-tailed, and values of <0.05 were regarded as statistically significant.

Results

Table 1 compares age-adjusted mean values and prevalences of selected cardiovascular risk factors at baseline according to serum glucose category. The prevalences of diabetic type were 3.7% for men and 2.4% for women, and the corresponding prevalences of borderline type were 20.6% and 11.5%. Glucose abnormality was positively associated with many other cardiovascular risk factors for both sexes.

During follow-up, we documented 170 incident coronary heart disease (98 men and 72 women), 113 incident myocardial infarctions (71

Table 1
Age-adjusted mean values or prevalences of risk factors at baseline according to serum glucose category in non-fasting subjects.

	Men				Women			
	Normal type	Borderline type	Diabetic type	*p* Value for difference	Normal type	Borderline type	Diabetic type	*p* Value for difference
No. at risk	2209	600	107		3802	509	105	
Age, year	52.3 (0.2)	52.5 (0.4)	56.2 (0.8)	<0.001	51.9 (0.1)	53.9 (0.4)	55.9 (0.8)	<0.001
Serum glucose, mmol/L	6.3 (0.0)	8.8 (0.0)	13.8 (0.1)	<0.001	6.2 (0.0)	8.7 (0.0)	14.6 (0.1)	<0.001
Body mass index, kg/m^2	22.7 (0.1)	23.0 (0.1)	23.2 (0.3)	0.008	23.2 (0.1)	23.8 (0.1)	24.7 (0.3)	<0.001
Systolic blood pressure, mmHg	135 (0.4)	142 (0.8)	139 (2.0)	<0.001	132 (0.3)	139 (0.9)	143 (1.9)	<0.001
Diastolic blood pressure, mmHg	82 (0.3)	84 (0.5)	83 (1.2)	0.002	79 (0.2)	80 (0.5)	81 (1.1)	0.010
Antihypertensive medication, %	10.6	15.3	16.9	0.001	10.9	16.4	20.8	<0.001
Hypertension, %	42.4	52.6	55.1	<0.001	35.6	48.7	59.4	<0.001
Serum total cholesterol, mmol/L	4.73 (0.02)	4.80 (0.04)	4.85 (0.08)	0.129	5.01 (0.01)	5.18 (0.04)	5.28 (0.09)	<0.001
Serum triglycerides, mmol/L	1.68 (0.03)	1.80 (0.05)	2.23 (0.13)	<0.001	1.48 (0.01)	1.59 (0.04)	2.07 (0.09)	<0.001
Serum HDL-cholesterol, mmol/L	1.44 (0.01)	1.49 (0.02)	1.45 (0.05)	0.111	1.50 (0.01)	1.50 (0.02)	1.41 (0.05)	0.183
Current smokers, %	64.3	68.7	76.1	0.009	7.3	7.4	10.8	0.402
Ex-smokers, %	16.5	15.3	4.8	0.005	1.1	0.5	2.6	0.128
Ethanol intake, g/day	27.1 (0.6)	31.9 (1.1)	29.9 (2.7)	<0.001	1.4 (0.1)	1.5 (0.4)	0.4 (0.8)	0.440
Postmenopausal, %	–	–	–		57.0	57.8	57.3	0.862

In parentheses; standard errors. HDL-cholesterol; high-density lipoprotein cholesterol.

men and 42 women), 624 censored out of the community (193 men and 431 women) and 2,260 deaths (1,174 men and 1,086 women).

For reference, the corresponding results among fasting subjects or among fasting and non-fasting ones were shown in Supplemental Table 1.

Table 2 shows the relationship between serum glucose category and risks of coronary heart disease and myocardial infarction. Multivariable HRs of coronary heart disease for diabetic type were approximately 2 to 3 and were statistically significant for women and for total subjects. The HRs of myocardial infarction for diabetic type tended to be higher than those of coronary heart disease and were statistically significant except for men. The HRs of coronary heart disease associated with one standard deviation increment of serum glucose were statistically significant for men, for women and for total subjects. The results were much the same in myocardial infarction.

For reference, the corresponding results among fasting subjects or among fasting and non-fasting ones were showed in Supplemental Table 2.

When we excluded the subjects who took medication for diabetes mellitus ($n=26$, 12% of diabetic type), the results did not change substantially, that is, the multivariable HRs (95% CI) for risk of coronary heart disease for diabetic type were 2.40 (1.02–5.67) for men, 3.64 (1.58–8.42) for women and 2.86 (1.58–5.15) for total subjects. The corresponding HRs (95% CI) of myocardial infarction were 2.53 (0.98–6.57), 6.00 (2.32–15.50) and 3.55 (1.85–6.84). When we restricted the subjects to <3 h postprandial status ($n=6,321$, 86.2% of total non-fasting subjects), the results did not change substantially. The multivariable HRs for risk of coronary heart disease for diabetic type were 1.81 (0.71–4.64) for men, 3.53 (1.51–8.26) for women and 2.46 (1.33–4.56) for total subjects. The corresponding HRs of myocardial infarction were 1.79 (0.62–5.14), 6.14 (2.34–16.08) and 3.07 (1.54–6.10). When we adjusted further for HDL-cholesterol levels among a subsample in which the data on HDL-cholesterol were available ($n=4,385$, 59.8% of total non-fasting subjects), the multivariable HRs for risk of coronary heart disease for diabetic type were 2.61 (0.76–8.94) for men, 2.73 (0.33–22.95) for women and 2.20 (0.78–6.22) for total subjects. The corresponding HRs of myocardial infarction were 3.43 (0.97–12.19), 4.08 (0.38–44.21) and 3.11 (1.06–9.12).

Discussion

The community-based observational study presented here shows that non-fasting glucose concentration, either as diagnosis of diabetic

Table 2
Multivariable hazard ratios (HRs, 95% CI) of coronary heart disease and myocardial infarction according to serum glucose category and glucose concentration in non-fasting subjects.

	Person years	Coronary heart disease			Person years	Myocardial infarction		
		No of events	Age adjusted HR (95% CI)§	Multivariable HR (95% CI)		No of events	Age adjusted HR (95% CI)§	Multivariable HR (95% CI)
Men								
Normal type	45,987	64	Ref.	Ref.	46,176	47	Ref.	Ref.
Borderline type	12,233	28	1.65 (1.06–2.57)*	1.41 (0.89–2.25)	12,304	19	1.52 (0.90–2.60)	1.24 (0.71–2.16)
Diabetic type	1674	6	2.44 (1.05–5.65)*	1.98 (0.84–4.68)	1674	5	2.86 (1.13–7.22)*	2.14 (0.83–5.55)
HR per 1SD increment of glucose	59,894	98	1.24 (1.09–1.41)†	1.17 (1.02–1.36)*	60,154	71	1.27 (1.10–1.46)†	1.18 (1.00–1.38)
Women								
Normal type	85,565	51	Ref.	Ref.	85,946	28	Ref.	Ref.
Borderline type	11,628	14	1.89 (1.04–3.41)*	1.49 (0.80–2.75)	11,712	8	1.91 (0.87–4.21)	1.40 (0.61–3.18)
Diabetic type	2105	7	4.90 (2.21–10.87)‡	3.39 (1.47–7.81)†	2129	6	7.76 (3.18–18.92)‡	5.70 (2.21–14.67)‡
HR per 1SD increment of glucose	99,298	72	1.30 (1.14–1.48)‡	1.19 (1.03–1.38)*	99,787	42	1.39 (1.20–1.61)‡	1.27 (1.07–1.50)†
Total								
Normal type	131,552	115	Ref.	Ref.	132,122	75	Ref.	Ref.
Borderline type	23,860	42	1.74 (1.22–2.49)†	1.49 (1.03–2.15)*	24,016	27	1.66 (1.07–2.58)*	1.35 (0.85–2.13)
Diabetic type	3779	13	3.34 (1.88–5.96)‡	2.47 (1.37–4.46)†	3803	11	4.44 (2.35–8.40)‡	3.17 (1.65–6.10)‡
HR per 1SD increment of glucose	159,191	170	1.26 (1.15–1.38)‡	1.19 (1.08–1.32)‡	159,941	113	1.32 (1.19–1.46)‡	1.22 (1.09–1.37)‡

Test for significance: *$P<0.05$, †$P<0.01$, ‡$P<0.001$. §: Age and sex adjusted HR for total subjects.
Multivariable hazard ratio adjusted for age, sex, community, sex-specific quartiles of body mass index, of serum triglycerides, serum total cholesterol, hypertensive status, antihypertensive medication use, cigarette smoking status, alcohol intake category, time since last meal and for women, menopausal status.

type or as continuous variable, is an independent significant predictor for incident coronary heart disease and myocardial infarction in middle-aged general population. A prospective study of Japanese representative sample (Kadowaki et al., 2008) ($n=9,444$, mean follow-up period 17.3 years) investigated the association between casual (combined fasting and non-fasting) blood glucose and mortality from coronary heart disease for men and women combined. In that study, the multivariable HRs (95% CI) of coronary heart disease mortality were 2.43 (1.29–4.58) for borderline high casual blood glucose (7.77 to <11.10 mmol/L) and 2.62 (1.46–4.67) for high casual blood glucose (≥11.10 mmol/L) compared with lower blood glucose levels (<5.22 mmol/L). Another Japanese study (Saito et al. 2011) ($n=31,192$, median follow-up period 12.9 years) showed a similar result on the excess risk of coronary heart disease associated with borderline and diabetes mellitus, but it showed no significant association between non-fasting glucose concentration, neither as diagnosis of diabetic type nor as continuous variable, and the risk of coronary heart disease. Our results were inconsistent with that previous study. However, in the present study, the follow-up period was longer (22 years vs. 12.9 years) and the percentage of non-fasting blood samples in whole subjects was higher (74.1% vs. 57.5%) than the previous study. Therefore this study may have been able to detect the association.

The HRs of coronary heart disease and of myocardial infarction for subjects with diabetic type were greater for women than for men. Our finding extended the evidence from an Italian prospective study of type 2 diabetic patients, which showed that blood glucose 2 h after lunch, but not fasting blood glucose was a significant predictor for cardiovascular events, particularly in women (Cavalot et al. 2006). Although women seem to be more susceptibility to hyperglycemia for the risk of coronary heart disease, additional research is needed to clarify the sex difference mechanism.

The multivariable HRs (95% CI) of coronary heart disease for subjects with borderline type were 1.49 [1.03–2.15]. It is consistent with the result of a previous meta-analysis of 38 prospective observational studies dealing with postload glucose, casual glucose, fasting glucose or hemoglobin A1c (Levitan et al., 2004). It identified nondiabetic hyperglycemia as a risk marker for cardiovascular disease (HR 1.19, [95% CI, 1.07–1.32]). Further follow up is necessary to examine the effect of borderline type on risk of myocardial infarction.

The mechanisms for the progression of atherosclerosis by non-fasting hyperglycemia were suggested by several animal studies. The repetitive postprandial fluctuations in glucose concentrations of diabetic rats induced by being fed twice daily were found to generate the monocyte adhesion to endothelial cells of the thoracic aorta even at lower hemoglobinA1c levels (mean values were less than 4.0%) (Azuma et al., 2006). Further, the repetitive postprandial glucose spikes in apolipoprotein E-deficient mice induced by being fed maltose, accelerated the macrophage adhesion to endothelial cells and the formation of fibrotic arteriosclerotic lesions (Mita et al., 2007). Diabetic rats produced by inducing insulin-mediated rapid "glycemic swings" (exaggeratedly changing blood glucose levels), regardless of their effect on average blood glucose levels, have impaired endothelium-dependent relaxation, in part via enhanced activation of the poly(ADP-ribose) polymerase pathway (Horváth et al., 2009). In another study, oxidative stress, estimated from 24 h urinary excretions rates of unbound 8-iso-prostaglandin F2α, was correlated with acute glucose fluctuations but not with hemoglobinA1c or fasting glucose concentration (Monnier et al., 2006).

The strength of the current study was population-based cohort study based on the standardized epidemiological methods, so that our findings may be more appropriate to generalize. Second, we used incident coronary heart disease or myocardial infarction as the target endpoint because it reflects more directly the relationship with risk factors than does mortality from coronary heart disease or myocardial infarction.

Conclusion

Our population-based cohort study of Japanese showed that non-fasting glucose concentration, either as diagnosis of diabetic type or as continuous variable, proved to be an independent predictor for incident coronary heart disease and myocardial infarction.

The CIRCS Investigators are the following: Yoshinori Ishikawa, Akihiko Kitamura, Masahiko Kiyama, Masakazu Nakamura, Takeo Okada, Masakazu Nakamura, Masatoshi Ido, Kenji Maeda, Mitsumasa Umesawa, Isao Muraki, Yuji Shimizu, Takashi Shimamoto, Minoru Iida and Yoshio Komachi, Osaka Medical Center for Health Science and Promotion; Shinichi Sato, Chiba Prefectural Institute of Public Health; Yoshihiko Naito, Mukogawa Women's University; Hideki Ozawa, Oita University Faculty of Medicine; Kazumasa Yamagishi, Choy-Lye Chei and Tomoko Sankai, Graduate School of Comprehensive Human Sciences, University of Tsukuba; Tetsuya Ohira, Hironori Imano, Renzhe Cui, Ai Ikeda, Satoyo Ikehara, Koutatsu Maruyama, Yoshimi Kubota and Hiroyasu Iso, Osaka University Graduate School of Medicine; Hiroyuki Noda, Osaka University Hospital; Takeshi Tanigawa, Isao Saito, Susumu Sakurai, Shinichi Hitsumoto and Masamitsu Konishi, Ehime University Graduate School of Medicine.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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研究代表者　　岡村 智教
〒160-8582
東京都新宿区信濃町35
慶應義塾大学医学部衛生学公衆衛生学
TEL:03-3353-1211FAX:03-3359-3686

印　　刷　　有限会社MOA
〒105-0004
東京都港区新橋2-10-3ブラザービル8F
TEL:03-3500-3248FAX:03-3591-3370