Predicting Coronary Heart Disease Using Risk Factor Categories for a Japanese Urban Population, and Comparison with the Framingham Risk Score: The Suita Study

Kunihiro Nishimura[1], Tomonori Okamura[2], Makoto Watanabe[1], Michikazu Nakai[1], Misa Takegami[1], Aya Higashiyama[3], Yoshihiro Kokubo[1], Akira Okayama[4] and Yoshihiro Miyamoto[1]

[1]Department of Preventive Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan
[2]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan
[3]Department of Environmental and Preventive Medicine, Hyogo College of Medicine, Hyogo, Japan
[4]The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo, Japan

Aim: The Framingham risk score (FRS) is one of the standard tools used to predict the incidence of coronary heart disease (CHD). No previous study has investigated its efficacy for a Japanese population cohort. The purpose of this study was to develop new coronary prediction algorithms for the Japanese population in the manner of the FRS, and to compare them with the original FRS.
Methods: Our coronary prediction algorithms for Japanese were based on a large population-based cohort study (Suita study). Study subjects comprised initially 5,886 healthy Japanese. They were followed-up for 11.8 years on average, and 213 cases of CHD were observed. Multiple Cox proportional hazard model by stepwise selection was used to construct the prediction model.
Results: Our coronary prediction algorithms for Japanese patients were based on a large population-based cohort study (the Suita study). The study comprised 5,886 initially healthy Japanese subjects. They were followed-up for 11.8 years on average, and 213 cases of CHD were observed. A multiple Cox proportional hazard model by stepwise selection was used to construct the prediction model. The C-statistics showed that the new model had better accuracy than the original and recalibrated Framingham scores. The net reclassification improvement (NRI) by the Suita score with the inclusion of CKD was 41.2% ($P<0.001$) compared with the original FRS. The recalibration of the FRS slightly improved the efficiency of the prediction, but it was still worse than the Suita score with the CKD model. The calibration analysis suggested that the original FRS and the recalibrated FRS overestimated the risk of CHD in the Japanese population. The Suita score with CKD more accurately predicted the risk of CHD.
Conclusion: The FRS and recalibrated FRS overestimated the 10-year risk of CHD for the Japanese population. A predictive score including CKD as a coronary risk factor for the Japanese population was more accurate for predicting CHD than the original Framingham risk scores in terms of the C-statics and NRI.

J Atheroscler Thromb, 2014; 21:000-000.

Key words: Coronary heart disease, Risk score, Japanese cohort, Framingham risk score, Suita study

Address for correspondence: Kunihiro Nishimura, Department of Preventive Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan, 5-7-1, Fujishiro-dai, Suita, Osaka, 565-8565 Japan
E-mail: knishimu@res.ncvc.go.jp
Received: May 7, 2013
Accepted for publication: February 4, 2014

Introduction

The Framingham Heart Study identified the classic risk factors for coronary heart disease (CHD)[1], and it developed multivariable predictive instruments, which enable clinicians to estimate the 10-year individual risk of developing CHD[2, 3]. These findings have also been widely adopted in clinical guidelines[4, 5]. However, the FRS cannot be generalized for other populations, since 99% of the Framingham cohort participants were Caucasian[5]. For example, the use of the FRS in some other populations resulted in an overestimation of the CHD risk[6-8].

There has been relatively little attention paid to the validity of the FRS in the Japanese population, which constitutes a unique population in many aspects, with a markedly lower incidence of CHD than Western populations[9]. To our knowledge, no previous Japanese cohort study has been performed to evaluate the original and recalibrated FRS.

Several Japanese cohort studies developed risk prediction tools for Japanese patients. The NIPPON DATA 80 prediction tool has been used as the standard prediction tool in Japan[10], and has been adopted by some clinical guidelines for the stratification of risk in Japanese subjects[11]. However, the NIPPON DATA 80's outcome measure was coronary death, not the incidence of CHD. The Hisayama study predicted a composite outcome of stroke and CHD[12]. Noda's prediction score also applied to cardiac mortality[13]. The JALS study group developed a prediction tool for acute myocardial infarction (AMI), but their prediction period was relatively short (five years)[14]. The JMS-cohort study chart was also targeted for AMI, but the population was limited to rural residents[15]. These tools are all associated with some advantages and disadvantages. However, additional tools for the prediction of CHD are needed that can accurately assess the risk of the longer-term incidence of CHD in the Japanese population.

In this context, we have developed a new algorithm, named the Suita Score, for predicting the 10-year probability of developing CHD, which is based on the findings of a large population-based cohort study performed in an urban area in Japan.

Furthermore, chronic kidney disease (CKD) has recently been advocated as an independent risk factor for CHD, and patients with CKD tend to possess multiple CVD risk factors, and thus represent a major public health problem[16, 17]. A recent CHD risk assessment tool based on 2.3 million patients, the QRISK2, included CKD as a necessary component for the risk prediction[18]. Moreover, CKD patients tend to have an underestimated CHD risk based on the FRS[19]. In addition, we previously reported that CKD leads to an increased risk of both MI and stroke[20]. Hence, the objective of this study was;

1) To incorporate established classic coronary risk factors into newly developed coronary prediction algorithms for the Japanese population,

2) To compare the discriminatory properties of this approach with those of the original and recalibrated FRS

Methods

Populations

The Suita study, a cohort study of urban residents in Japan, was started in 1989. It was based on a random sampling of 12,200 Japanese residents living in Suita. As a baseline, participants between the ages of 30 and 79 years of age were randomly selected from the municipality population registry in 1989. Of these, 6485 males and females underwent regular health checkups between September 1989 and March 1994. The subjects have continued to visit the National Cerebral and Cardiovascular Center (NCVC) every two years for regular health checkups[21-24]. A total of 1,546 subjects were excluded from the study based on a past history of CHD or stroke, non-fasting blood collections, missing data or because they were lost to follow-up. The data from the remaining 5,866 participants (2,788 males and 3,078 females) were used for the analyses. This cohort study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Baseline Examinations

Blood samples were collected after the participants had fasted for at least 10 hours. The samples were centrifuged immediately, and a routine blood examination was performed that included the serum total cholesterol (TC), high density lipoprotein cholesterol (HDLC), triglycerides (TG), serum creatinine (Cre) and fasting blood glucose (FBG) levels. The blood pressure was measured three times on the right arm after five minutes of rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used for the analyses. Public health nurses obtained information on the smoking and drinking habits and medical histories. To ensure comparability with the FRS, the categorization of the BP, diabetes, TC and HDL-C in this study were done in accordance with the criteria used in the FRS model3. DM was defined as an FBG level $\geq$ 7.0 mmol/L (126 mg/dl) and/or current use of anti-diabetic medication. Cigarette smoking was dichotomized as current versus non-current. The LDL-C was determined by the Freidewald equation.

Definition of CKD

The serum Cre level was measured using the noncompensated kinetic Jaffe′ method. The estimated glomerular filtration rate (eGFR) of each participant was calculated from Cre value and the age, using the MDRD equation below, modified with the Japanese coefficient (0.881)[25]:

eGFR (ml/min/1.73 m2) = $0.881*186*age^{-0.203}*Cre^{-1.154}$ (for males)

eGFR = $0.881*186*age^{0.203}*Cre^{-1.154}*0.742$ (for females).

The CKD stage was defined by the K/DOQI clinical practice guidelines[26]. CKD was categorized into Stage 3 CKD (eGFR 30-60 ml/min/1.73m^2) and Stage 4 or 5 CKD (eGFR < 30 ml/min/1.73m^2).

Endpoint Determination

The follow-up method used in the Suita study has been reported previously[20-24]. The endpoints for the current follow-up study were: (1) the date of the first diagnosis of CHD (2) the date of death, (3) the date when the subject left Suita or (4) censoring by December 31, 2007.

The first step in the survey for CHD involved checking the health status of all the participants at clinical visits carried out every two years, and by yearly questionnaires sent by mail or conducted by telephone. The second step involved the review of in-hospital medical records of participants who were suspected to have developed CHD. The criteria for definite or probable acute myocardial infarction were the same as the criteria used for the MONICA project[27].

In order to complete the surveillance for fatal MI, we also conducted a systematic search of death certificates. In addition to acute myocardial infarction, the criteria for a diagnosis of CHD included sudden cardiac death within 24 hours after the onset of acute symptoms, or CHD followed by coronary artery bypass or angioplasty.

Statistical Analysis

First, we evaluated the validity of categorical variables in the Suita Score to compare them with the original FRS[3]. Then, we conducted a multiple Cox proportional hazard model using the same categories as those in the FRS. Subsequently, we developed a new CHD risk score for Japanese subjects based on the Cox model for the Suita cohort. Other risk factors were calculated using the same categories as the FRS. A stepwise selection with a *p*-value of 0.1 for backward elimination was used to select the best predictive model.

After selection of the best Cox model, we fitted the hazard functions developed by the Framingham investigators from the previously published data[6] for predicting the 10-year probability of developing CHD in the Suita cohort. The probability function was: $P = 1 - S(t)\ {}^\wedge exp(X, M)$; $f(X, M) = \beta_1*(X_1 - M_1) + \ldots + \beta_n*(X_n - M_n)$,

where S(t) is the survival rate for the mean values of the risk factors at 10 years in the Suita study; $\beta_1 \ldots \beta_n$ are the regression coefficients of the Cox model (β) shown in **Table 3** ; $X_1 \ldots X_n$ represent the individual risk factor values of each study participant and $M_1 \ldots M_n$ are the mean values of the risk factors in the Suita cohort. In the recalibrated Framingham functions, the coefficients were taken from the Framingham Cox model, but the mean values from the Suita cohort were used for the risk factors and the mean incidence rates[6].

Discrimination and calibration were used to evaluate the predictive capabilities of the models. We evaluated the discriminatory ability of this model by comparing the means of the C-statistics and Bayesian information criteria (BIC). Furthermore, we measured the model improvement as indicated by the clinical reclassification of the FRS by the Suita Score, which is considered to be more important indicator for predictive ability using the net reclassification improvement (NRI)[28]. Since the inclusion of a new biomarker in a prediction tool , such as the FRS, minimally improves the predictive ability, the evaluation based on the NRI is considered to be a valid approach for evaluating the new biomarker[29]. The NRI measures the reclassification of people from one risk category to another resulting from the addition of the new risk factor to a prediction model with established risk. If all of the people end up in a more correct risk class based on the model with the new marker, the NRI is positive. We calculated the category-free NRI[30].

The third approach was calibration, which measured how closely the predicted risk fit the actual risk. The Suita participants were divided into quintiles of 10-year CHD risk predicted by the Suita score functions, the original Framingham functions and the recalibrated Framingham functions[6]. The predicted and actual risk in each quintile were compared, and the differences were assessed by the Hosmer-Lemeshow chi-square tests. The SAS software program, version 9.3. (SAS Institute Inc), and the STATA software program, version 12 (STATA Corp LP), were used for all of the statistical analyses.

Results

Population Characteristics

The number of person-years studied consisted of 75,776 (34,480 for males and 41,296 for females),

Table 1. Population characteristics of the study cohort

	Males (n=2796)	Females (n=2725)
Age (years, mean ± SD)	56.1 ± 13.3	54.5 ± 12.9
DM (%)	6	5.8
Current smoker (%)	49.67	11.91
Blood pressure (mmHg, %)		
Optimal (SBP < 120, DBP < 80)	30.74	41.68
Normal (SBP < 130, DBP < 85)	19.31	17.30
High normal (SBP < 140, DBP < 90)	17.98	15.69
Stage I HT (SBP < 160, DBP < 100)	20.39	15.94
Stage II to IV HT (SBP < 160, DBP ≥ 100)	11.59	9.40
Total cholesterol (mg/dl, %)		
< 160	10.12	6.88
160-199	39.75	30.52
200-239	37.41	39.60
240-279	10.98	18.51
≥ 280	1.74	4.49
LDL cholesterol (mg/dl, %)		
> 130	55.54	45.78
130-159	28.19	30.86
> 160	16.26	23.34
HDL cholesterol (mg/dl, %)		
< 35	11.40	3.28
35-44	28.71	16.36
45-49	15.87	12.25
50-59	23.82	29.95
≥ 60	20.20	38.14
Creatinine (mg/dl, mean ± SD)	0.91 ± 0.21	0.69 ± 0.22
eGFR (mean ± SD)	64.7 ± 24.9	90.6 ± 29.3
CKD (≥ Stage 3) (%)	46.2	11.3

LDL, Low-density lipoprotein; HDL, high-density lipoprotein;
eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); CKD, chronic kidney disease; HT, hypertension

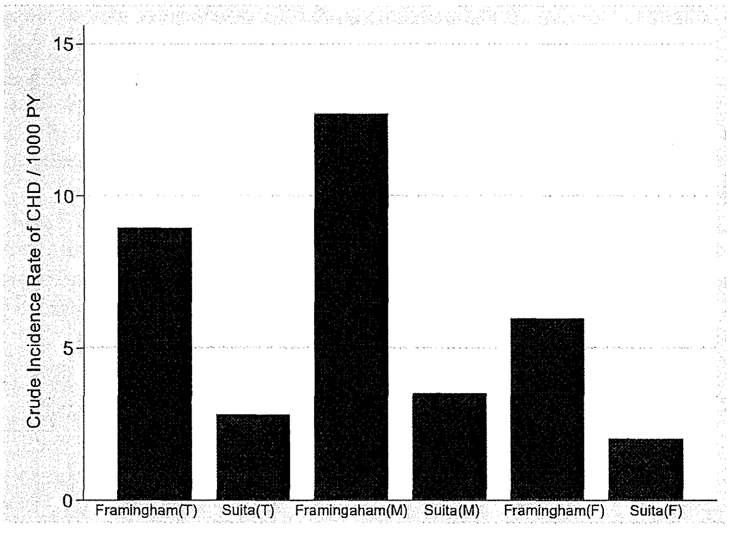

Fig. 1. The absolute risk difference of the Framingham cohort and Suita Study cohort

The Framingham cohort data were adopted from Wilson's study
CHD, coronary heart disease; PY, person-years; Framingham(T), total Framingham cohort; Framingham(M), Male Framingham cohort; Framingham(F), Female Framingham cohort; Suita(T), total Suita cohort; Suita (M), Male Suita cohort; Female Suita (F), Suita cohort

Table 2. The multivariable-adjusted hazard ratios for coronary heart disease based on the FRS categories

MALES				
Variable	Relative Risk	*P*-value	95% CI	Framingham Cohort
Age, y	1.07	<0.001	1.05-1.09	1.05
TC, mg/dl				
<200	Reference			
200-239	1.30	0.172	0.89-1.88	1.31
≥ 240	2.15	0.001	1.38-3.34	1.9
HDL-C mg/dl				
<35	2.06	0.001	1.37-3.10	1.47
35-59	Reference			
≥ 60	0.67	0.103	0.42-1.08	0.56
Blood Pressure				
Normal (including optimal)	Reference			
High normal	1.52	0.104	0.92-2.51	1.31
Stage I hypertension	2.24	<0.001	1.45-3.46	1.67
Stage II hypertension	2.34	0.001	1.41-3.86	1.84
Diabetes (y/n)	1.39	0.234	0.81-2.40	1.5
Smoking	1.25	0.193	0.89-1.76	1.68
CKD	1.34	0.109	0.94-1.92	N.A
FEMALES				
Variable	Relative Risk	*P*-value	95% CI	Framingham Cohort
Age, y	1.10	<0.001	1.07-1.13	1.04
TC, mg/dl				
<200	Reference			
200-239	0.58	0.097	0.30-1.10	1.51
≥ 240	1.38	0.272	0.78-2.46	1.72
HDL-C mg/dl				
<35	1.94	0.102	0.88-4.31	2.02
35-59	Reference			
≥ 60	1.04	0.881	0.61-1.79	0.58
Blood Pressure				
Normal (including optimal)	Reference			
High normal	1.60	0.222	0.75-3.38	1.3
Stage I hypertension	1.82	0.089	0.91-3.61	1.73
Stage II hypertension	3.86	<0.001	1.99-7.48	2.12
Diabetes (y/n)	2.59	0.013	1.23-5.49	1.77
Smoking	3.22	<0.001	1.74-5.97	1.47
CKD	1.38	0.247	0.80-2.40	N.A

FRS, Framingham risk score; All variables were adjusted for all FRS variables by a Cox proportional hazard model. CKD, chronic kidney disease; 95% CI, 95% confidence interval; N.A, not available

with a mean follow-up period of 11.8 years. During the follow-up period, there were 213 incidents of CHD. The population characteristics are summarized in **Table 1**. The univariate Cox regression analysis indicated all variables in FRS were statistically significant (data not shown).

Fig. 1 depicts the difference in the absolute risk for CHD between the Framingham cohort and Suita study cohort. The crude incidence rate of CHD in the original Framingham cohort was 8.94 per 1000 person-years, while that of the Suita cohort was 2.81 per 1000 person-years. The risk of developing CHD is nearly one-third of both the males and females in this study cohort.

The results of the multiple Cox proportional hazard model using the same categories as those used in the FRS are shown in **Table 2**. All hazard ratios (HRs) of categorical hypertension were higher than those of the original FRS. The HRs of smoking and DM for females were also higher than those of the original FRS (2.59 and 3.22, respectively). The HR of a TC between 200 and 239 for females was 0.58, which was lower than that of the FRS. The HRs of other variables were similar to those of the original FRS.

Prediction Model Development and the Simplified Prediction Model for Clinical Use

Table 3 shows the best Cox model for the Suita cohort selected by a stepwise method with the total cholesterol categories. (TC Suita score) The multivariable adjusted HR for the association between CHD and Stage 3 CKD was 1.39 and that for Stage 4 and 5 CKD was 3.72, respectively. The HRs of the other predictors were similar between the with CKD and without CKD models.

Table 4 shows the best Cox model for the Suita Score with CKD according to the cut-off levels of LDL-C and HDL-C proposed in the Japan Atherosclerosis Society (JAS) Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases 2012[11, 31] (LDL Suita Score). For convenient clinical use, we developed prediction sheets based on the TC and LDL Suita Scores (**Table 5**). The beta coefficients corresponding to the Cox model were multiplied 10 times for categorical covariates and were rounded. For the age category, the midpoint of each category was multiplied by the β coefficients in **Table 4**, and then multiplied 10 times. We added all these values corresponding to each individual risk, divided the number by 10, and then the corresponding probability of CHD was calculated from the equation: P = 1 − S(t)^exp((sum of the points)/10) where S(t) is the baseline survival function of the Suita cohort.

The C-statistics of the LDL Suita Score with CKD in **Table 4**, which corresponded to the AUC of the Cox proportional hazard model, was 0.831. This was very similar to the TC Suita Score shown in **Table 3**, which had a C-index of 0.835 (**Table 6a**). The likelihood ratio test was not conducted, since the categorical variables were different and these two models were not nested. The NRI between TC Suita Score with CKD and the LDL Suita Score with CKD was not significant (P=.0.256; **Table 6b**). These findings suggest that the two models predict CHD with similar efficiency.

Validation of the Inclusion of CKD

The C-static of the Suita Score without CKD was slightly lower than the Suita Score with CKD (0.835 vs. 0.833). The comparison between the TC Suita Scores with and without CKD suggested that the addition of CKD improved the risk classification of CHD by 40%. This suggested that the inclusion of CKD in the risk prediction tool improves the prediction of the development of CHD, making it a more appropriate predictive tool.

Comparison of the Suita Score and Framingham Risk Scores

Table 7a shows the model fit, C-statistics and BIC of the Cox regression for the TC Suita Score, the original FRS and the recalibrated score for the mean value of each of the covariates. The TC Suita Score with CKD showed the best goodness-of-fit by the likelihood ratio test, and the C-statistics of the TC Suita Score with CKD were also the highest. The BIC was the lowest for the TC Suita Score with CKD, which supported its better predictive ability. The C-statistics were not changed by the recalibration of the FRS. The C-statistics of the recalibrated FRS were still smaller than the TC Suita Score with CKD.

The results of the clinical reclassification measured by the NRI are shown in **Table 7b**. The NRI for the TC Suita Score with CKD compared to the original FRS was 46.8% (P<0.001). In both the CHD and non-CHD groups, the risk categories tended to be increased by the TC Suita Score with CKD. The NRI between the TC Suita Score with CKD and the recalibrated model was lower (25.4%), but the difference remained significant (P=0.003). These associations also held for the TC Suita Score without CKD, the FRS and the recalibrated FRS.

Fig. 2 depicts the actual and predicted probabilities of the 10-year risk of cardiac events by calibration. The FRS consistently overestimated the cardiac events in all quintiles. The overall 10-year calibration of the FRS and recalibrated FRS were worse than the TC Suita Score with CKD as determined by the Hosmer-Lemeshow chi-square test (both p<0.001). The largest difference between the actual rate and the predicted rate after recalibration was 13.9% (in the fifth quintile in males), compared with the difference of 14.5% for the FRS. The difference between the actual probability and the TC Suita Score with CKD was not significant (P=0.18). The TC Suita Score with CKD model underestimated the risk of CHD in the fourth quintile, but the difference was only 2.2%. These findings consistently indicated that the FRS overestimates the CHD risk in the Japanese population.

Table 3. The Cox regression coefficients for the Suita cohort adjusted for the original FRS variables (TC Suita Score)

3a. TC Suita Score with CKD

	β	HR	*P*-value	95% CI
Age, years	0.0766382	1.08	<0.001	1.06-1.10
Female	−0.5866078	0.56	0.001	0.39-0.78
Smoking	0.4865127	1.63	0.002	1.20-2.21
DM	0.4557071	1.59	0.042	1.02-2.45
Blood Pressure				
Optimal	−0.7183575	0.49	0.003	0.31-0.78
Normal and high normal	Referent	Reference	Reference	Reference
Stage I hypertension	0.3330895	1.40	0.055	0.99-1.96
Stage II hypertension	0.59332684	1.81	0.002	1.25-2.63
TC (mg/dl)				
<160	−1.112393	0.33	0.008	0.14-0.74
160-239	Referent	Reference	Reference	Reference
240-279	0.5110573	1.67	0.003	1.19-2.32
Over 280	0.8511397	2.34	0.002	1.36-4.04
HDL(mg/dl)				
<35	0.6173452	1.85	0.001	1.27-2.71
35-50	Referent	Reference	Reference	Reference
50-59	−0.5096169	0.60	0.008	0.41-0.87
Over 60	−0.4322771	0.65	0.022	0.45-0.94
CKD				
Stage 3	0.3278965	1.39	0.035	1.02-1.88
Stage 4 or 5	1.315004	3.72	0.005	1.48-9.38

3b. TC Suita Score without CKD

	β	HR	*P*-value	95% CI
Age, years	0.0806456	1.08	<.0001	1.07-1.10
Female	−0.7401036	0.48	<.0001	0.35-0.66
Smoking	0.4527364	1.57	0.004	1.16-2.14
DM	0.424255	1.52	0.059	0.98-2.37
Blood Pressure				
Optimal	−0.7017837	0.50	0.004	0.31-0.79
Normal and high normal	Referent	Reference	Reference	Reference
Stage I hypertension	0.3607005	1.43	0.037	1.02-2.01
Stage II hypertension	0.6305927	1.87	0.001	1.30-2.72
TC (mg/dl)				
<160	−1.073273	0.34	0.010	0.16-0.78
160-239	Referent	Reference	Reference	Reference
240-279	0.5408852	1.71	0.001	1.23-2.40
Over 280	0.8678275	2.38	0.002	1.38-4.10
HDL(mg/dl)				
<35	0.6742382	1.96	<.0001	1.35-2.86
35-50	Referent	Reference	Reference	Reference
50-59	−0.5011838	0.61	0.009	0.44-0.93
Over 60	−0.4464421	0.64	0.018	0.15-0.93

CKD, chronic kidney disease; TC, total cholesterol; LDL, low density lipoprotein; 95% CI, 95% confidence interval; CKD, chronic kidney disease; HR, hazard ratio; all other abbreviations are the same as in Table 1. The gender difference was incorporated into the model as a covariate to improve the predictability of the model.

Table 4. The LDL Suita Score with CKD model according to the JAS Guideline 2012 LDL/HDL cut-off (n=5,727) (LDL Suita Score)

4a. The LDL Suita Score with CKD

	β	HR	P-value	95% CI
Age, years	0.0760078	1.08	<0.001	1.06-1.10
Female	−0.6619839	0.52	<0.001	0.36-0.74
Smoking	0.5031949	1.65	0.002	1.20-2.28
DM	0.5533678	1.74	0.031	1.05-2.88
Blood Pressure				
Optimal	−0.6763825	0.51	0.005	0.32-0.82
Normal and high normal	Reference	Reference	Reference	Reference
Stage I hypertension	0.4189501	1.52	0.019	1.07-2.16
Stage II hypertension	0.5935986	1.81	0.001	1.22-2.68
LDL (mg/dl)				
<100	Reference	Reference	Reference	Reference
100-140	0.5319015	1.70	0.039	1.03-2.81
140-160	0.6837867	1.98	0.015	1.14-3.43
160-180	1.021015	2.78	<0.001	1.57-4.91
Over 180	1.128479	3.09	<0.001	1.69-5.66
HDL(mg/dl)				
<40	Reference	Reference	Reference	Reference
40-59	−0.4730423	0.62	0.005	0.45-0.87
≥ 60	−0.5822414	0.56	0.007	0.37-0.85
CKD				
Stage 3	0.2893668	1.34	0.071	0.98-1.83
Stage 4 or 5	1.388216	4.01	0.008	1.43-11.25

4b. The LDL Suita Score without CKD

	β	HR	P-value	95% CI
Age, years	0.0795083	1.08	<0.001	1.06-1.10
Female	−0.804252	0.45	<0.001	0.32-0.62
Smoking	0.4642934	1.59	0.004	1.16-2.19
DM	0.3955565	1.48	0.106	0.91-2.40
Blood Pressure				
Optimal	−0.6602255	0.52	0.006	0.32-0.83
Normal and high normal	Reference	Reference	Reference	Reference
Stage I hypertension	0.4467296	1.56	0.012	1.10-2.21
Stage II hypertension	0.6256262	1.87	0.002	1.27-2.76
LDL (mg/dl)				
<100	Reference	Reference	Reference	Reference
100-140	0.5040579	1.66	0.049	1.00-2.74
140-160	0.664678	1.94	0.017	1.57-4.90
160-180	1.01949	2.77	<0.001	1.73-4.90
Over 180	1.151674	3.16	<0.001	1.73-5.80
HDL (mg/dl)				
<40	Reference	Reference	Reference	Reference
40-59	−0.4798994	0.62	0.004	0.45-0.86
≥ 60	−0.6092216	0.54	0.005	0.36-0.83

JAS Guideline 2012, Japan Atherosclerosis Society(JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012; CKD, chronic kidney disease; LDL, low density lipoprotein; 95% CI, 95% confidence interval; CKD, chronic kidney disease; HR, hazard ratio; all other abbreviations are the same as in Table 1. Stage 3 and Stage 4 or 5 CKD were defined by estimated GFR levels of 30-60 ml/min/1.73 m^2 and less than 30 ml/min/1.73 m^2, respectively.

Table 5. Prediction score sheets for TC/ LDL Suita score

5a. TC Suita scoore

Risk Factor Variable	Score
Age	
36-45	30
46-55	39
56-65	46
>65	58
Female	-6
Current Smoker	5
DM	5
Blood pressure	
Optimal blood pressure	-7
Normal and high normal	0
Stage 1 hypertension	3
Stage 2 hypertension	9
TC (mg/dl)	
<160	-11
160-239	0
240-279	5
>280	9
HDL (mg/dl)	
<35	6
36-49	0
50-59	-5
>=60	-5
CKD	
eGFR>60	0
Stage 3	3
Stage 4 or 5	15
Total Score	A

Predicted Probability of CHD in 10 years

Total Score	Probability (%)
30<=	<1
31-35	1
36-40	2
41-45	4
46-50	6
51-55	10
56-60	15
>=61	24

5b. LDL Suita Score

Risk Factor Variable	Score
Age	
35-44	30
45-54	38
55-64	45
65-69	51
>=70	53
Female	-7
Current Smoker	5
DM	6
Blood pressure	
Optimal blood pressure	-7
Normal and high normal	0
Stage 1 hypertension	4
Stage 2 hypertension	6
LDL (mg/dl)	
<100	0
100-139	5
140-159	7
160-179	10
>=180	11
HDL (mg/dl)	
<40	0
40-59	-5
>=60	-6
CKD	
eGFR>60	0
Stage 3	3
Stage 4 or 5	14
Total Score	A

Predicted Probability of CHD in 10 years

Total Score	Probability (%)
35<=	<1
36-40	1
41-45	2
46-50	3
51-55	5
56-60	9
61-65	14
66-70	22
71<	>28

Estimates risk for CHD over a period of 10 years based on Suita Cohort experience at baseline. Summation of risk factor category points yield total score. JAS Guideline 2012, Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012. LDL cholesterol was derived by Fridewald's equation. Those who have triglycerides>400 were omitted for the calculation.

Discussion

In this study, we demonstrated the predictive ability of newly developed coronary prediction algorithms for Japanese subjects developed in the manner of the FRS. Our findings can be summarized as follows: 1) the risk profile for CHD of a Japanese population was considerably different from that of the original Framingham Heart Study cohort; 2) The prediction of CHD obtained with the risk score based on the Suita cohort with CKD variables was superior to that of the FRS or recalibration of the FRS; 3) Clinical reclassification revealed that the FRS overestimates the CHD risk in the Japanese population.

First, the risk profile of the Suita cohort proved to be considerably different from that of a Western population. The crude incidence rate of CHD in the original Framingham Cohort was 8.94 per 1000 person-years, while that of the Suita cohort was only 2.81 per 1000 person-years. The risks of hypertension, low HDL-C for males, and diabetes and smoking for females, in the Suita cohort were weighted higher than the risks in the Framingham cohort. This difference between the Suita and the Framingham cohorts constitutes a major concern for the application of the FRS in Japanese subjects, where the lower CHD incidence

Table 6. Validation of the inclusion of CKD in the TC Suita Score and LDL Suita Score

6a.

Model	Log Likelihood	LR test, *p*-value	C-statistics	BIC
TC Suita Score with CKD	−1610.8	referent	0.835	3233.3
TC Suita Score without CKD	−1618.1	0.013	0.833	3238.5
LDL Suita Score with CKD	−1510.1	referent	0.831	3365.6
LDL Suita Score without CKD	−1513.6	0.032	0.829	3414.5

6b.

Model		TC Suita Score with CKD	LDL Suita Score with CKD	LDL Suita Score with CKD
Reference Model		TC Suita Score without CKD	LDL Suita Score without CKD	TC Suita Score with CKD
Cases	Reclassified Downward (%)	16.7	48.1	48.8
	Reclassified Upward (%)	83.3	51.9	51.2
Non Cases	Reclassified Downward (%)	36.7	26.1	43.8
	Reclassified Upward (%)	63.3	73.9	56.2
Category-free NRI(%)		40.0	43.9	10.1
P-value		<0.001	<0.001	0.256

6a, Comparison of the C-index , LR test and BIC results demonstrating the discrimination for CHD prediction models based on the Suita Score with and without CKD, the FRS and the FRS calibrated for the means of the Suita cohort. Log likelihoods were derived from the multivariate adjusted Cox proportional hazard model.; CKD, chronic kidney disease; FHS, Framingham Heart Study; LR test, likelihood ratio test; BIC, Bayesian information criteria
6b, Comparison of the FRS and Suita Scores and the corresponding reclassification rate for the prediction of CHD events during a 10-year period;. NRI, net reclassification improvement

and different risk factor levels were observed[32-34].

Second, the discriminatory capability of the TC Suita Score with CKD is better than those of the original and recalibrated FRS. Although recalibration with the mean value of the risk factors and baseline survival functions for the study cohort improved the discriminatory capability for various ethnic groups in the U.S., China and the CKD population[6, 12, 16], the recalibration did not improve the discriminatory capability in Japanese subjects. We believe this is probably due to the low incidence of CHD in Japan compared to Western and Chinese populations[35]. The relative risks of various factors were similar between Suita Study cohort and the Framingham cohort. Therefore, the difference between the two prediction tools heavily depends on the difference in the absolute risks between these two cohorts. Accordingly, the clinical reclassification pointed out that the FRS overestimated the risk of CHD in Japanese subjects, especially in the non-CHD group, since the baseline survival function, which was higher than that in the original FRS, affected the estimated risk in an exponential manner and the overestimation was more severe in the high risk groups.

Furthermore, we found that CKD is an independent risk factor for CHD after adjusting for other predictors of the FRS. The cohorts in the Framingham Heart Study and the Offspring study showed no significant association between the presence of kidney disease and the incidence of CVD[36] although some collaborative analyses showed positive associations[17, 37]. Our result is essentially compatible with that of Weiner's study, which reported the HRs of CKD after adjustment of the FRS for whites and blacks[38]. No previous study has dealt with this association for Asian ethnicity as an additional covariate in the prediction tool, although many cohort studies in Japan have demonstrated a significant association between CKD and cardiovascular disease[20, 25, 39].

Finally, we developed a simple prediction sheet for the estimation of CHD based on the TC and LDL Suita Score. For the exact estimation, the beta-coefficient from the TC and LDL Suita Score are preferable. However, the calculation requires computational

Table 7. A comparison of the predicted risks in models based on the Framingham risk score and Suita Score with and without CKD

7a.

Model	Log Likelihood	LR test, p-value	C-statistics	BIC
TC Suita Score with CKD	−1610.8	referent	0.835	3233.3
TC Suita Score without CKD	−1618.1	0.013	0.833	3238.5
Original Framingham Score	−1678.5	<0.001	0.768	3365.6
Recalibrated Framingham Score	−1702.9	<0.001	0.740	3414.5

7b.

Model		TC Suita Score with CKD	TC Suita Score with CKD	TC Suita Score without CKD	TC Suita Score without CKD
Reference Model		Original Framingham Score	Recalibrated Framingham Score	Original Framingham Score	Recalibrated Framingham Score
Cases	Reclassified Downward (%)	42.0	50.0	42.8	49.3
	Reclassified Upward (%)	58.0	50.0	57.2	50.7
Non Cases	Reclassified Downward (%)	65.4	63.1	65.4	63.2
	Reclassified Upward (%)	34.6	36.9	34.6	37.0
Category-free NRI(%)		46.8	25.4	45.3	27.5
P-value		<0.001	0.002	<0.001	0.001

7a, Comparison of the C-index, LR test and BIC results demonstrating the discrimination for CHD prediction models based on the Suita Score with and without CKD, the FRS and the FRS calibrated for the means of the Suita cohort. The log likelihoods were derived from the multivariate adjusted Cox proportional hazard model.; CKD, chronic kidney disease; FHS, Framingham Heart Study; LR test, likelihood ratio test; BIC, Bayesian information criteria

7b, A comparison of the FRS and Suita Scores and the corresponding reclassification rate for the prediction of CHD events during a 10-year period;. NRI, net reclassification improvement

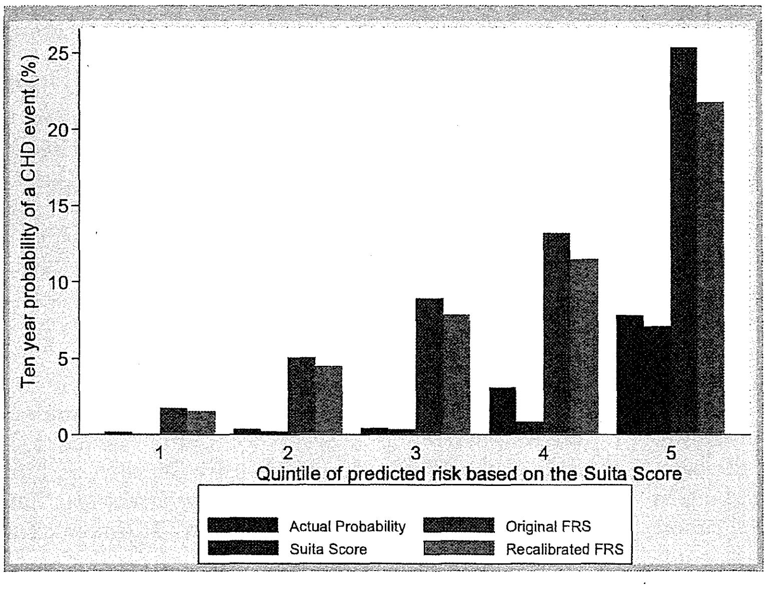

Fig. 2. The ten-year prediction of CHD events in the Suita study using the TC Suita Score with CKD

A graphical representation of the actual 10-year risk of cardiac events in the Suita cohort, along with the predicted risk and the Framingham risk function with and without recalibration for the means of the Suita cohort stratified by the quintile of predicted risk in the Suita cohort. The Suita participants were divided into quintiles of 10-year CHD risk predicted by the Suita score functions with CKD in Table 3. In each quintile, the mean predicted 10-year probabilities and actual probabilities were estimated. The Suita Score, the Suita Score with CKD shown in Table 3. FRS, Framingham risk score. CHD, coronary heart disease.

power, and the more simplified tool is as effective in the clinical setting as the original FRS, since both the models use beta coefficients and a simplified clinical score.

The incorporation of CKD yields limited improvement in the predictive capability in terms of C-statistics. However, the NRI and IDI showed marked improvement by the incorporation of CKD, which is a more clinically relevant index for prediction improvement. These two methods are becoming more popular and widely used in cardiovascular medicine[40, 41] For example, incorporating the homocysteine level into the FRS was evaluated by the NRI[42], since the inclusion of a new biomarker to the existing CHD risk score changed the predictability of events in a very marginal manner (less than 0.01 of the AUC)[43], and an enormously large odds ratio is needed for significant improvement[44, 45]. Clinicians currently do not have a tool for evaluating the CHD risk of patients with CKD but with relatively few other risk factors. These patients might be misjudged as having a very low risk.

Recently, an individualized risk prediction tool including more diverse risk factors increased 43% AMI and Strokes at the same cost[46]. Therefore, we believe that the inclusion of CKD in the prediction score is necessary and effective for populations at high risk for CHD. Currently, there are estimated to be more than 11 million CKD patients in Japan[47], and people have little doubt that CKD has a major impact on the population's health.

Our population had higher risks for developing CHD compared to other Japanese cohorts. The Suita cohort population was selected from an urban population, in contrast to the majority of other cohorts in Japan, which have been selected mainly from rural populations. Because approximately 66% of the Japanese population lives in urban areas according to 2006 Japanese Census[48], this is an important feature of our analysis. Interestingly, the JMS cohort and JALS reported that the crude incidence of AMI was 0.68 and 0.60 per 1000 person-years, respectively[11, 14, 15, 49]. On the contrary, the crude incidence of AMI in the Suita study was 1.40[50]. These findings may suggest that there is a large difference in the incidence of CHD between rural and urban areas in Japan. Thus, our tool is more useful for predicting the risk in urbanized populations with a higher risk of CHD.

Our study is associated with several limitations. First, the single assessment of risk factors at the baseline survey may have led to a regression dilution bias[51]. Second, the response rate of the original cohort was 53.1% (6,825/ 12,200) although the participants were randomly selected from the population of Suita city. In addition, based on the urbanized nature of the study population, it may not be possible to apply this tool in the whole Japanese population. However, since the outcome of the Suita study was the development of CHD, we believe that this tool can be a complement to the NIPPON DATA 80 risk score adopted in the JAS 2012 guidelines[11], in which the outcome was CHD mortality. The external validation of our score must be evaluated in other cohort studies, although a lack of external validation is a common problem with the existing Japanese risk prediction tools, including the NIPPON DATA 80, JALS, JMS cohort and Hisayama study. Considering the increasingly Westernized lifestyle in urban areas[52], these tools should be re-evaluated using a consortium of cohort studies, which include both urban and rural areas, such as the Epoch-Japan study group[53].

Very recently, the new AHA/ACC Guideline on the Treatment of Blood Cholesterol recommended the use of the new Pooled Cohort Equations to estimate the 10-year CHD risk in both white and black males and females, aged 40-75 years, and the FRS is no longer used for risk assessment[54]. However, this guideline is known to inaccurately estimate the CHD risk for Asians, Therefore, the value of the Suita Score for Japanese subjects and other low risk Asian populations is still superior to other systems.

Third, besides CKD, new biomarkers that can predict the CHD risk are emerging[55-57]. However, our study could not access their importance as have other existing prediction tools for Japanese subjects. For, example, the QRISK included rheumatoid arthritis, atrial fibrillation and the BMI. These relatively common, but not classic, cardiac risk factors must also be evaluated in future studies.

In conclusion, for Japanese subjects, the Suita prediction score with the CKD category resulted in better CHD prediction than the original and recalibrated FRS.

Conflict of Interest Disclosures

None.

Funding

The present study was supported by an Intramural Research Fund (22-4-5) for Cardiovascular Diseases of the NCVC, Comprehensive Research on Life-style-Related Diseases, Including Cardiovascular Diseases and Diabetes Mellitus: H23-Junkankitou ([Seishuu]-Ippan-005)

References

1) Dawber TR, Kannel WB, Revotskie N, Stokes J, 3rd, Kagan A, Gordon T: Some factors associated with the development of coronary heart disease: Six years' follow-up experience in the framingham study. Am J Public Health Nations Health, 1959; 49: 1349-1356
2) Wilson PW, Castelli WP, Kannel WB: Coronary risk prediction in adults (the framingham heart study). Am J Cardiol, 1987; 59: 91G-94G
3) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. Circulation, 1998; 97: 1837-1847
4) Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D: Prevention of coronary heart disease in clinical practice: Recommendations of the task force of the european society of cardiology, european atherosclerosis society and european society of hypertension. Atherosclerosis, 1994; 110: 121-161
5) Third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii) final report. Circulation, 2002; 106: 3143-3421
6) D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P: Validation of the framingham coronary heart disease prediction scores: Results of a multiple ethnic groups investigation. JAMA, 2001; 286: 180-187
7) Thomsen TF, McGee D, Davidsen M, Jorgensen T: A cross-validation of risk-scores for coronary heart disease mortality based on data from the glostrup population studies and framingham heart study. Int J Epidemiol, 2002; 31: 817-822
8) Hense HW, Schulte H, Lowel H, Assmann G, Keil U: Framingham risk function overestimates risk of coronary heart disease in men and women from germany--results from the monica augsburg and the procam cohorts. Eur Heart J, 2003; 24: 937-945
9) Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T: Cardiovascular disease and risk factors in asia: A selected review. Circulation, 2008; 118: 2702-2709
10) Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a japanese representative population. Circ J, 2006; 70: 1249-1255
11) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K: Executive summary of the japan atherosclerosis society (jas) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in japan -2012 version. J Atheroscler Thromb, 2013; 20: 517-523
12) Arima H, Yonemoto K, Doi Y, Ninomiya T, Hata J, Tanizaki Y, Fukuhara M, Matsumura K, Iida M, Kiyohara Y: Development and validation of a cardiovascular risk prediction model for japanese: The hisayama study. Hypertens Res, 2009; 32: 1119-1122
13) Noda H, Iso H, Sairenchi T, Irie F, Fukasawa N, Toriyama Y, Ota H, Nose T: [prediction of stroke, coronary heart disease, cardiovascular disease, cancer, and total death based on results of annual health checkups]. Nippon Koshu Eisei Zasshi, 2006; 53: 265-276
14) Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, Ando T, Ueshima H, Group. JALS: Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events - the jals-ecc. Circ J, 2010; 74: 1346-1356
15) Matsumoto M, Ishikawa S, Kayaba K, Gotoh T, Nago N, Tsutsumi A, Kajii E: Risk charts illustrating the 10-year risk of myocardial infarction among residents of japanese rural communities: The jms cohort study. J Epidemiol, 2009; 19: 94-100
16) Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med, 2004; 351: 1296-1305
17) Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: A pooled analysis of community-based studies. J Am Soc Nephrol, 2004; 15: 1307-1315
18) Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, Brindle P: Predicting cardiovascular risk in england and wales: Prospective derivation and validation of qrisk2. BMJ (Clinical research ed.), 2008; 336: 1475-1482
19) Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ: The framingham predictive instrument in chronic kidney disease. Journal of the American College of Cardiology, 2007; 50: 217-224
20) Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, Higashiyama A, Kamide K, Kawanishi K, Okayama A, Kawano Y: Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban japanese population with and without chronic kidney disease: The suita study. Stroke, 2009; 40: 2674-2679
21) Higashiyama A, Okamura T, Ono Y, Watanabe M, Kokubo Y, Okayama A: Risk of smoking and metabolic syndrome for incidence of cardiovascular disease--comparison of relative contribution in urban japanese population: The suita study. Circ J, 2009; 73: 2258-2263
22) Kokubo Y, Okamura T, Yoshimasa Y, Miyamoto Y, Kawanishi K, Kotani Y, Okayama A, Tomoike H: Impact of metabolic syndrome components on the incidence of cardiovascular disease in a general urban japanese population: The suita study. Hypertens Res, 2008; 31: 2027-2035
23) Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y: Impact of high-normal blood pressure on the risk of cardiovascular disease in a japanese urban cohort: The suita study. Hypertension, 2008; 52: 652-659
24) Watanabe M, Okamura T, Kokubo Y, Higashiyama A, Okayama A: Elevated serum creatine kinase predicts first-ever myocardial infarction: A 12-year population-based cohort study in japan, the suita study. Int J Epidemiol,

2009; 38: 1571-1579
25) Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S: Estimation of glomerular filtration rate by the mdrd study equation modified for japanese patients with chronic kidney disease. Clin Exp Nephrol, 2007; 11: 41-50
26) K/doqi clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis, 2002; 39: S1-S266
27) Monica manual. Cvd/mnc/version 1.1, 1986 dec. Geneva: WHO. 1987: 1-104 (S-104)
28) Cook NR: Statistical evaluation of prognostic versus diagnostic models: Beyond the roc curve. Clinical chemistry, 2008; 54: 17-23
29) Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU, Lindemans J, Hofman A, Steyerberg EW, van der Lugt A, van den Meiracker AH, Witteman JC: Evaluation of newer risk markers for coronary heart disease risk classification: A cohort study. Ann Intern Med, 2012; 156: 438-444
30) Pencina MJ, D'Agostino RB, Sr., Steyerberg EW: Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med, 2011; 30: 11-21
31) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K: Diagnostic criteria for dyslipidemia. J Atheroscler Thromb, 2013; 20: 655-660
32) Tuomilehto J, Kuulasmaa K: Who monica project: Assessing chd mortality and morbidity. Int J Epidemiol, 1989; 18: S38-S45
33) Keil U, Kuulasmaa K: Who monica project: Risk factors. Int J Epidemiol, 1989; 18: S46-S55
34) Liu J, Hong Y, D'Agostino RB, Sr., Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D: Predictive value for the chinese population of the framingham chd risk assessment tool compared with the chinese multi-provincial cohort study. JAMA, 2004; 291: 2591-2599
35) Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, et al.: Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. JAMA, 1995; 274: 131-136
36) Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. Kidney Int, 1999; 56: 2214-2219
37) Weiner DE, Tabatabai S, Tighiouart H, Elsayed E, Bansal N, Griffith J, Salem DN, Levey AS, Sarnak MJ: Cardiovascular outcomes and all-cause mortality: Exploring the interaction between ckd and cardiovascular disease. Am J Kidney Dis, 2006; 48: 392-401
38) Weiner DE, Tighiouart H, Griffith JL, Elsayed E, Levey AS, Salem DN, Sarnak MJ: Kidney disease, framingham risk scores, and cardiac and mortality outcomes. Am J Med, 2007; 120: 552 e551-e558
39) Higashiyama A, Watanabe M, Kokubo Y, Ono Y, Okayama A, Okamura T: Relationships between protein intake and renal function in a japanese general population: Nippon data90. J Epidemiol, 2010; 20 Suppl 3: S537-S543
40) Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, Go AS, Harrell FE, Jr., Hong Y, Howard BV, Howard VJ, Hsue PY, Kramer CM, McConnell JP, Normand SL, O'Donnell CJ, Smith SC, Jr., Wilson PW: Criteria for evaluation of novel markers of cardiovascular risk: A scientific statement from the american heart association. Circulation, 2009; 119: 2408-2416
41) Duprez DA, Jacobs DR, Jr., Lutsey PL, Bluemke DA, Brumback LC, Polak JF, Peralta CA, Greenland P, Kronmal RA: Association of small artery elasticity with incident cardiovascular disease in older adults: The multi-ethnic study of atherosclerosis. Am J Epidemiol, 2011; 174: 528-536
42) Veeranna V, Zalawadiya SK, Niraj A, Pradhan J, Ference B, Burack RC, Jacob S, Afonso L: Homocysteine and reclassification of cardiovascular disease risk. Journal of the American College of Cardiology, 2011; 58: 1025-1033
43) Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS: Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med, 2006; 355: 2631-2639
44) Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P: Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol, 2004; 159: 882-890
45) Ware JH: The limitations of risk factors as prognostic tools. N Engl J Med, 2006; 355: 2615-2617
46) Eddy DM, Adler J, Patterson B, Lucas D, Smith KA, Morris M: Individualized guidelines: The potential for increasing quality and reducing costs. Ann Intern Med, 2011; 154: 627-634
47) Nephrology JSo: Guideline of ckd diagnosis and treatment 2009; 2012
48) Kanemoto Y KR: Urban employment areas: Defining japanese metropolitan areas and constructing the statistical database for them. CRC Taylor & Francis; 2006
49) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K: Absolute risk of cardiovascular disease and lipid management targets. Journal of atherosclerosis and thrombosis, 2013
50) Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A: Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban japanese cohort study: The suita study. Atherosclerosis, 2009; 203: 587-592
51) MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J: Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias.

Lancet, 1990; 335: 765-774
52) Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H: Trend of westernization of etiology and clinical characteristics of heart failure patients in japan--first report from the chart-2 study. Circ J, 2011; 75: 823-833
53) Nagasawa S-y, Okamura T, Iso H, Tamakoshi A, Yamada M, Watanabe M, Murakami Y, Miura K, Ueshima H, Group ftEfCPfOCiJR: Relation between serum total cholesterol level and cardiovascular disease stratified by sex and age group: A pooled analysis of 65 594 individuals from 10 cohort studies in japan. Journal of the American Heart Association, 2012; 1
54) Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW: 2013 acc/aha guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the american college of cardiology/american heart association task force on practice guidelines. Circulation, 2013
55) Hasokawa M, Shinohara M, Tsugawa H, Bamba T, Fukusaki E, Nishiumi S, Nishimura K, Yoshida M, Ishida T, Hirata K: Identification of biomarkers of stent restenosis with serum metabolomic profiling using gas chromatography/mass spectrometry. Circ J, 2012; 76: 1864-1873
56) Saito I, Kokubo Y, Kiyohara Y, Doi Y, Saitoh S, Ohnishi H, Miyamoto Y: Prospective study on waist circumference and risk of all-cause and cardiovascular mortality. Circ J, 2012; 76: 2867-2874
57) Nakajima K, Matsuo S, Okuyama C, Hatta T, Tsukamoto K, Nishimura S, Yamashina A, Kusuoka H, Nishimura T: Cardiac event risk in japanese subjects estimated using gated myocardial perfusion imaging, in conjunction with diabetes mellitus and chronic kidney disease. Circ J, 2012; 76: 168-175

JCP Digest

Journal of Clinical Periodontology 2014:41

Paper Digest 05

EFP European Federation of Periodontology
Periodontal Health for a better life

Scientific release from the European Federation of Periodontology

Rapporteurs: Seelam N, with Davideau JL, Tenenbaum H, and Huck O.

Link to Original JCP article :
http://onlinelibrary.wiley.com/doi/10.1111/jcpe.12241/full
Access through EFP members page login:
http://www.efp.org/members/jcp.php

Affiliation: Prepared by residents from the Postgraduate Program of Periodontology at the Dept. of Periodontology, Dental Faculty, University of Strasbourg, Strasbourg, France.

Study:

The effect of periodontal status and occlusal support on masticatory performance: the Suita study

Kosaka T, Ono T, Yoshimuta Y, Kida M, Kikui M, Nokubi T, Maeda Y, Kokubo Y, Watanabe M, Miyamoto Y.
J Clin Periodontol. 2014: 41; 487-503.

Summarised from original article with kind permission from Wiley Online Library

Relevant background to study:

Several risk factors such as tooth loss, occlusal support and maximum "bite force", have been demonstrated to directly affect masticatory ability. Decrease in masticatory ability adversely affects nutritional intake and negatively impacts upon quality of life. Previous studies have shown that periodontal tissue destruction may also reduce masticatory ability. However, few studies have investigated this issue, taking into account occlusal support especially in elderly patients with a reduced number of teeth.

Study Aims:

To evaluate the influence of periodontal status on masticatory performance in dentate subjects with identical areas of occlusal support.

Methods:

This prospective cohort study recruited 1839 elderly patients (67.2 ± 7.9 years) selected randomly from the Suita study that was established to promote prevention of cardiovascular diseases in Japan. Number of functional teeth and occlusal support were evaluated using the "Eichner index" (A1-3, B1-4, C1-3 groups). Periodontal status was assessed using the Community Periodontal Index (CPI), coded from 0 to 4, by means of partial mouth recording (10 index teeth). Masticatory performance was objectively evaluated by optical density measurement of the glucose concentration released from a "gummy jelly" and correlated with the surface area of the masticated test jelly. Results were adjusted for age and gender. Subjects for whom masticatory performance could not be accurately measured were excluded.

Results:

- A large number of enrolled subjects were classified as Eichner A1 (n=653) without missing teeth and with occlusal contacts in all posterior areas. In this group, 54.1% of subjects had no periodontal pockets (CPI = 0-2).
- Teeth with periodontal pockets (CPI ≥ 3) represented 30% of the Eichner A1 group while this proportion increased to 70% in Eichner B3 group (occlusal contacts in one posterior area).
- In Eichner groups A1 and B3, patients with moderate and severe periodontitis (CPI = 3-4) showed reduced masticatory performance in comparison with those without periodontitis (CPI = 0-2). No significant differences were highlighted in other Eichner A and B groups.
- The proportion of subjects wearing dentures increased from Eichner A2 group (8.3%) to Eichner B4 group (93.4%) and associated with a significant decrease of occlusal support.
- Masticatory performance of denture wearers from Eichner B2 and B3 groups decreased respectively in subjects with moderate periodontitis (B2) and in subjects with moderate and severe periodontitis (B3) in comparison with those without periodontitis.
- When only non-denture wearers were considered, no significant differences in masticatory performance was observed in Eichner A2 to B3 groups according to periodontal status.

Continue . . .

JCP Digest

Scientific release from the European Federation of Periodontology

Journal of Clinical Periodontology 2014:41

Paper Digest 05

EFP European Federation of Periodontology
Periodontal Health for a better life

Conclusions, impact and limitations:

Conclusions:
- Worsening of periodontal status affects masticatory performance in elderly people.
- The influence of periodontal status upon masticatory performance could be observed in patients without tooth loss and also in denture wearers.

Practical considerations:
- Periodontal screening and treatment associated with prosthetic rehabilitation in elderly subjects may improve masticatory performance and consequently lead to a better quality of life.

Limitations:
- Periodontal status was only evaluated on the basis of CPI and by means of partial mouth recording, and the latter is known to underestimate disease prevalence. A more precise evaluation of periodontal parameters including bleeding on probing, clinical attachment and bone levels, and mobility would provide additional data related to inflammatory status, periodontal diagnosis and their influence on masticatory performance.
- Due to the random selection of patients, discrepancies among the sample size of each Eichner groups led to low statistical power for small sample sized groups
- No data were provided regarding alveolar ridge or denture quality in subjects with tooth loss. Such parameters may have affected the evaluation of masticatory performance

ORIGINAL ARTICLE

Additive Interaction of Oral Health Disorders on Risk of Hypertension in a Japanese Urban Population: The Suita Study

Yoshio Iwashima,[1] Yoshihiro Kokubo,[2] Takahiro Ono,[3] Yoko Yoshimuta,[3] Momoyo Kida,[3] Takayuki Kosaka,[3] Yoshinobu Maeda,[3] Yuhei Kawano,[1] and Yoshihiro Miyamoto[2]

BACKGROUND
This study assessed the relationship between different oral health markers—periodontitis, gingival bleeding, tooth number, and occlusal status—and hypertension in a Japanese urban population.

METHODS
A total of 1,643 participants with no prior cardiovascular disease (mean age = 66.6 years; 43.4% women) underwent comprehensive health checkups, including a lifestyle questionnaire and dental examination in the Suita Study.

RESULTS
In the multivariable-adjusted logistic model, none of the individual oral health markers, namely severe periodontitis, gingival bleeding, lowest quartile of tooth number, and malocclusion, were significantly associated with increased odds of hypertension. The additive effects of oral health markers on hypertension were examined and showed that, compared with subjects with no component of the oral health markers, the multivariale-adjusted odds ratio of hypertension in those with ≥3 components was 1.82 (95% confidence interval (CI) = 1.23–2.72; $P = 0.003$). In the subpopulation without antihypertensive medication (n = 1,148; 59.8% women), a significant graded relationship between multivariable-adjusted systolic blood pressure and the number of components was found ($P_{trend} = 0.03$), and, compared with subjects with no component of the oral health markers, having ≥3 components was related to a higher systolic blood pressure ($\beta = 5.41$; 95% CI = 1.16–9.66; $P = 0.01$).

CONCLUSIONS
There is an additive relationship between oral health disorders and risk of hypertension. Our results suggest that the existence of moderate or severe oral health disorders—that is, several concomitant oral health disorders—is associated with risk of hypertension.

Keywords: blood pressure; hypertension; life style; oral health disorder; risk factor.

doi:10.1093/ajh/hpt227

Several epidemiological surveys have suggested the existence of a positive relationship between oral health disorders and hypertension.[1–5] Among such disorders, periodontitis is a common chronic infectious disease of the adult population, characterized by an exaggerated gingival inflammatory response against pathogenic bacterial microflora. If left untreated, it leads to deterioration of the supportive tissue of the teeth and eventually to tooth loss.[6] Periodontal disease, gingival bleeding, and tooth loss have been reported to be associated with hypertension,[1–5,7,8] and the systemic inflammatory response that may accompany these conditions has been implicated as a mechanism in the development of hypertension.[9] Periodontal disease and subsequent tooth loss may lead to poor dietary habits, or vice versa, and patients with these conditions may be likely to favor soft carbohydrate foods[10] and restrict fruit intake,[11] which influences blood pressure.[12] The modification of diet that occurs with these conditions has been speculated to be another possible mechanism in the development of hypertension;[9,13] however, the clinical implication of lifestyle variables such as eating habits or physical activity in the association between oral health disorders and hypertension remains to be elucidated. Further, tooth loss could contribute to worse occlusal status or masticatory performance, which is also an important pathological condition in oral health disorders; however, the influence of worse occlusal status on hypertension is also unknown.

In an effort to enrich understanding in the emerging area of the association between oral health and hypertension, we investigated the potential interrelationship between different markers of oral health, lifestyle variables, and risk of hypertension in a Japanese urban population.

Correspondence: Yoshio Iwashima (iwashima@hsp.ncvc.go.jp).

Initially submitted May 20, 2013; date of first revision June 21, 2013; accepted for publication November 10, 2013; online publication December 16, 2013.

Divisions of [1]Hypertension and Nephrology, and [2]Preventive Cardiology, Department of Medicine, National Cerebral and Cardiovascular Center, 5-7-1, Fujishirodai, Suita City, Osaka, Japan; [3]Department of Prosthodontics, Gerodontology and Oral Rehabilitation, Osaka University Graduate School of Dentistry, 1-8, Yamada-oka, Suita City, Osaka, Japan.

METHODS

Study subjects

The data used in this research derive from the Suita Study, which consisted of a random sample of Japanese urban residents. The details of this study are described elsewhere.[14–16] Briefly, 6,485 men and women aged 30–79 years had a baseline survey at the National Cardiovascular Center (now the National Cerebral and Cardiovascular Center) between September 1989 and March 1994 and underwent a medical examination every 2 years. Of these, 1,797 underwent comprehensive regular health checkups and dental examinations between June 2008 and March 2012. Participants in the study population were excluded from these analyses if they had a past or present history of cardiovascular disease, including ischemic heart disease, acute coronary syndrome, congestive heart failure requiring hospitalization, valvular heart disease requiring medication, stroke, history of transient ischemic attack (n = 88), or atrial fibrillation (n = 35), or had not undergone baseline dental examination (n = 31). After applying these exclusions, a total of 1,643 participants aged 30–79 years were available for this analysis. Physicians or nurses administered the questionnaire on individual personal habits and present illnesses. Informed consent was obtained from all participants. All participants were Japanese, and this study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M19-062-3).

Measurement of blood pressure and covariables

Well-trained physicians measured blood pressure twice in a seated position with an automated sphygmomanometer (Colin BP-I03ill; Omron, Kyoto, Japan) and an appropriately sized cuff according to a standard protocol after at least 5 minutes of rest before the initial blood pressure reading was obtained. Systolic (SBP) and diastolic (DBP) blood pressure were considered the average of 2 measurements recorded >1 minute apart. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or use of antihypertensive medication.

At the baseline examination, routine blood tests were performed, including triglycerides, high-density lipoprotein cholesterol, glucose, and hemoglobin A1c. Height and body weight were measured, and body mass index was calculated as weight (kg) divided by the square of height (m^2). Dyslipidemia was defined according to the guidelines of the National Cholesterol Education Program Third Adult Treatment Panel.[17] Diabetes mellitus was defined according to the American Diabetes Association criteria.[18] Estimated glomerular filtration rate was calculated using the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation in milliliters per minute per 1.73 m^2, as previously described.[19–21]

Oral examination

All participants received a complete oral examination by trained, certificated dentists. The periodontal condition was assessed using a modified Community Periodontal Index of Treatment Needs (CPITN)[22] in 8 designated molars (first and second molars) and 2 incisors (upper right and left central incisors) by applying the following scores: 0 indicates healthy periodontal tissue; 1 indicates gingival bleeding; 2 indicates calculus and/or overhanging restorations; 3 indicates pocket depth of 4–5 mm; and 4 indicates pocket depth of ≥6 mm. All periodontal examinations were performed by 4 experienced dentists, and the interobserver Cohen's kappa coefficient for grading was 0.78. The periodontal condition of every patient was reported as the worst CPITN condition. The presence or absence of gingival bleeding was also assessed by salivary occult blood test using a paper test strip (Salivaster; Showa Yakuhin, Tokyo, Japan).

The number of remaining teeth was counted in the full mouth with the exception of the third molars, which tend to be impacted, congenitally missing, or surgically removed because of anticipated pericoronitis.[23] Therefore, the maximum number of teeth was 28.

The status of occlusal support or masticatory performance was recorded by means of the Eichner index,[24] which is based on occlusal contact areas for the natural dentition in antagonist jaws, including fixed dentures. Class A contains 4 support zones; this means there is a minimum of 1 tooth in contact between the maxilla and the mandible in both the premolar and molar regions on each side. Class B contains 3, 2, or 1 support zone or support in the anterior area only. In class C, there are no antagonist contacts in the dentition.

Maximal bite force was measured by using the Dental Prescale System (GC, Tokyo, Japan), which consists of a horseshoe-shaped bite foil of pressure-sensitive film (50H, type R) and a computerized scanning system for analysis of the load.[25,26]

Lifestyle variables

Information on lifestyle was collected with a standardized questionnaire by physicians or nurses through face-to-face interviews, including demographic information such as smoking habit, dietary practices and usual frequency of food intake, exercise/sports and walking hours a day, and sleeping hours. Smoking status was defined as never smoker, former smoker, or current smoker. Alcohol consumption was categorized as none, social, or daily. Consumption of fruit and sugar-sweetened soft drinks was ascertained by questions as "fruit (citrus fruit, other fruit, and fresh fruit juice) intake ≥1 /day" and "sugar-sweetened soft drink intake ≥3 times /day," respectively. Sugar-sweetened soft drinks included all types of non-low-calorie, concentrated, carbonated, and ready-to-drink soft drinks. All low-calorie, no-added-sugar, and sugar-free types of concentrated, carbonated, and ready-to-drink soft drinks were not classified as sugar-sweetened soft drinks in this study. Physical activity was ascertained by question as"">1 hour walking or equivalent physical activity on average a day." Average sleep duration was classified into 8 categories: <4, 4–5, 5–6, 6–7, 7–8, 8–9, 9–10, and ≥10 hours per day.

Statistical analysis

Summary statistics are presented as mean (±SD) for continuous variables and as percentage for categorical

[redacted]

variables unless otherwise specified. First, the participants were divided into 2 groups according to the presence/absence of hypertension, and then the significance of any differences between groups was evaluated using unpaired *t* test or χ^2 test, as appropriate. Second, patients were stratified into 3 or 4 groups according to the status of oral health disorders. Differences in characteristics between groups were tested using χ^2 test for dichotomous variables and 1-way analysis of variance with Sheffe's post-test for continuous variables, as appropriate. Logistic regression analysis was used to determine the odds ratio (OR) of hypertension as a function of individual components of oral health markers, such as CPITN stage, gingival bleeding, tooth number, and Eichner index, as well as combinations of 2 oral health markers. In multivariable-adjusted models, we included variables that might confound the relationship between hypertension and oral health markers: age, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol consumption, daily fruit intake, daily sugar-sweetened soft drink intake, physical activity, and nocturnal sleep duration.

We next divided the subjects into 4 groups according to the number of oral health disorders present (0, 1, 2, or ≥3). The relative ORs of hypertension were assessed in age and sex-adjusted or multivariable-adjusted logistic regression models and calculated using the subgroup with no component of oral health markers as a reference for each. Differences in characteristics among the 4 groups were determined by 1-way analysis of variance with Scheffe's multiple comparison post-test for continuous variables and χ^2 test for categorical variables. Multivariable linear regression analyses using SBP or DBP as the dependent variable were also performed in the subjects not taking antihypertensive medication. Mean and SE were calculated in the case of linear regression, and OR and 95% confidence interval (CI) were calculated in the case of logistic regression. All *P* values were 2-sided, and those <0.05 were considered statistically significant. All of the calculations were performed using a standard statistical package (JMP 8.0; SAS Institute, Cary, NC; and SPSS version 17.0; SPSS, Chicago, IL).

RESULTS

General characteristics

The baseline characteristics of the study subjects are shown in Table 1. Mean age was 66.6 ± 7.9 years, and 43.4% of subjects were men. We first divided the subjects into 2 groups according to the presence/absence of hypertension and found that hypertensive subjects showed a significantly worse CPITN stage, higher prevalence of gingival bleeding, lower tooth number, and worse Eichner index.

Relations among oral health markers

To examine the relationships among oral health markers, we next divided the patients into 3 or 4 groups according to the status of oral health disorders (Table 2). There were significant trends toward higher prevalence of gingival bleeding, lower remaining tooth number, and worse Eichner index with increasing stage of CPITN. Similarly, there were significant trends toward higher prevalence of gingival bleeding, worse CPITN stage, and worse Eichner index with decreasing remaining tooth number. The Eichner index C group showed significantly lower remaining tooth number and worse CPITN stage than the Eichner A group (Table 2).

Relations of oral health disorders to hypertension

Age- and sex-adjusted logistic regression analysis found that only the presence of gingival bleeding was significantly associated with risk of hypertension, and the relation between individual oral health markers (CPITN stage 4, presence of gingival bleeding, lowest quartile of remaining tooth number, and Eichner index C) and hypertension was no longer significant throughout the adjustment process (Table 3). The Nagelkerke's adjusted R^2 value of the overall multivariable-adjusted logistic regression model without including oral health markers was 0.210 and was increased in the model after adding CPITN stage 4 (adjusted R^2 = 0.230), presence of gingival bleeding (adjusted R^2 = 0.230), lowest quartile of remaining tooth number (adjusted R^2 = 0.230), or Eichner index C (adjusted R^2 = 0.229).

Combined effects of oral health markers on hypertension

We next examined the combined effects of oral health markers on hypertension—that is, CPITN stage and gingival bleeding, CPITN stage and remaining tooth number, CPITN stage and Eichner index, gingival bleeding and remaining tooth number, gingival bleeding and Eichner index, and remaining tooth number and Eichner index. In the multivariable-adjusted logistic regression model, the combination of CPITN stage and gingival bleeding, the combination of CPITN stage and Eichner index, the combination of gingival bleeding and remaining tooth number, and the combination of gingival bleeding and Eichner index, but not the combination of CPITN stage and remaining tooth number and the combination of remaining tooth number and Eichner index, were independently associated with hypertension (Table 3).

The total subjects were then divided into 4 groups by the number of components of oral health markers, including CPITN stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C (Table 4). There was a significant graded relationship between the number of components present and the corresponding prevalence of hypertension. The age- and sex-adjusted relative OR of hypertension in subjects with 0, 1, 2, and ≥3 components of oral health disorders were 1.0 (reference), 1.06 (95% CI = 0.83–1.34; *P* = 0.66), 1.19 (95% CI = 0.87–1.63; *P* = 0.28), and 1.71 (95% CI = 1.18–2.49; *P* = 0.004). In multivariable-adjusted logistic regression analysis, subjects with ≥3 components of oral health disorders had 1.82 times higher odds of hypertension compared with those with no component (Figure 1). The adjusted R^2 value of the overall model after adding the number of components of oral health markers was 0.249.