proband, the coadministration of mexiletine with propranolol was efficacious, but this subject was also treated with ventricular pacing. Our study demonstrated additive effects of the 2 drugs at a pulsing frequency of 2 Hz (Figure 8). This observation suggested that a combination of mexiletine with propranolol in the setting of modest tachycardia were protective of ventricular arrhythmia caused by G1631D. We explain this effect by a combination of the intrinsic activity-dependent loss of channel availability observed for G1631D (Figure 4B) with the use-dependent drug effects.

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## Disclosures

None.

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## CLINICAL PERSPECTIVE

Mutations in *SCN5A* encoding the cardiac voltage-gated sodium channel have been associated with a spectrum of increased sudden death risk extending from fetal life to adulthood. We studied the functional and pharmacological properties of a novel de novo *SCN5A* mutation associated with an extremely severe perinatal presentation of congenital long-QT syndrome, characterized by late third trimester intrauterine fetal heart rhythm disturbances and life-threatening ventricular arrhythmia occurring within hours of emergency cesarean birth. The same mutation (G1631D), which was discovered in two subjects of different ethnic backgrounds with the same clinical presentation, caused a profound degree of sodium channel dysfunction that was more severe than that observed for any previous *SCN5A* variant. Despite the extreme nature of the mutation and the associated dire clinical scenario, the subjects survived owing to prompt therapeutic interventions, including treatment with the combination of mexiletine and propranolol, two drugs that exhibited enhanced and additive activity against the mutant allele. These observations illustrate the role of severe sodium channel mutations in a malignant perinatal variant of long-QT syndrome and successful use of combination pharmacotherapy to prevent perinatal mortality in this setting. Our data also illustrate the potential therapeutic benefits of a propranolol block of mutant sodium channels.

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# 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

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ABSTRACT

*Objective:* Only a small number of population-based cohort studies have directly compared the predictive value of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDLC) for coronary artery disease in Asian populations, such as Japan.
*Methods:* We performed an 11.9-year cohort study of 4694 men and women, aged 30–74 years, selected randomly from an urban general population in Japan. Baseline LDL-C levels were estimated using the Friedewald formula. The predictive values of LDL-C and non-HDLC for myocardial infarction (MI) and stroke were compared.
*Results and conclusion:* During the follow-up period, there were 80 incident cases of MI and 139 of stoke, comprised of 23 intracerebral hemorrhages, 85 cerebral infarctions and 31 other types of stroke. The Hazard ratio (HR) for MI was highest in the top quintile of LDL-C (HR: 3.03, 95% CI, 1.32–6.96) when male and female data were combined. The HR for MI was also highest in the top quintile of non-HDLC (HR: 2.97, 95% CI, 1.26–6.97). Analysis of trends showed a significant positive relationship between MI incidence and serum LDL-C and non-HDLC levels (both $P=0.02$). However, there was no relationship between the incidence of any subtype of stroke and either LDL-C or non-HDLC. The predictive value of LDL-C and non-HDLC for MI, assessed by calculating the differences in the −2 logarithm likelihood (−2 ln [L]) and area under the curve (AUC), were almost similar.

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## 1. Introduction

The causal relationship between high levels of serum low-density lipoprotein cholesterol (LDL-C) and coronary artery disease (CAD) is well established [1–5]. Blood LDL-C levels are therefore the main target for lipid management in the majority of guidelines of developed countries for preventing atherosclerotic disease [3–5]. Some US cohort studies have also suggested that non-high-density lipoprotein (non-HDLC) may be a better predictor of CAD [6,7]. However, to our knowledge, only one population-based cohort study has directly compared the predictive value of these lipid markers for CAD in an Asian population [8], which have a lower incidence of coronary artery disease, but a higher risk of stroke than Western populations [9–12]. Furthermore, although it has not been shown that there is a positive relationship between the risk of any type of stroke and high serum levels of total cholesterol (TC) in the Japanese population [9,10], the effects on stroke incidence of the closely related lipid fractions, LDL-C and non-HDLC, have not been evaluated.

The purpose of this study was therefore to investigate the predictive value of LDL-C and non-HDLC for the incidence of CAD and stroke in a Japanese urban population over an 11.9-year period. Our *a priori* hypothesis was that both LDL-C and non-HDLC may be useful predictors of CAD risk, but not of stroke risk.

## 2. Methods

### 2.1. Populations

The Suita study [13,14], a cohort study of cardiovascular disease, was established in 1989 and included 12,200 Japanese urban residents of Suita City, Osaka. The participants, aged 30–79 years,

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were selected randomly from the municipality population registry. Of these, 6485 men and women had a baseline medical examination at the National Cardiovascular Center between September 1989 and March 1994 (participation rate: 53.2%). Of the 6485 participants, a total of 1791 were excluded for the following reasons: past history of coronary heart disease or stroke ($n$ = 208), nonperiodical participation in baseline survey ($n$ = 79), aged 75 or older ($n$ = 343), non-fasting visit ($n$ = 153), use of lipid-lowering agents such as statins ($n$ = 106), serum triglyceride ≥4.5 mmol/l (400 mg/dl) ($n$ = 98) and missing information at the baseline survey or lost to follow-up ($n$ = 804). The data of the remaining 4694 participants (2169 men and 2525 women) were then analyzed. Informed consent was obtained from all participants. This cohort study was approved by the Institutional Review Board of the National Cardiovascular Center.

### 2.2. Baseline examination

Blood samples were collected at the National Cardiovascular Center (NCVC) after the participants had fasted for at least 12 h. The samples were centrifuged immediately and a routine blood examination that included serum total cholesterol (TC), HDL cholesterol, triglyceride and glucose levels then carried out. LDL-C was estimated using the Friedewald formula [15]. Non-HDLC was calculated by subtracting HDL-C from TC.

Blood pressures were measured in triplicate on the right arm in the seated position after 5 min rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used in the analyses. Hypertension was defined as either a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or the use of antihypertensive agents. Diabetes was defined as a fasting serum glucose ≥7.0 mmol/l (126 mg/dl), the use of anti-diabetic agents, or both. Height in stockings and weight in light clothing were measured. Public health nurses obtained information on the smoking, drinking and medical histories of the participants.

### 2.3. Endpoint determination

The participants were followed until December 31, 2005. The first step in the survey involved checking the health status of all participants by repeated clinical visits every 2 years and yearly questionnaires sent by mail or conducted by telephone. Informed consent for review of in-hospital medical records was obtained from 86.2% participants who were suspected of having had a myocardial infarction (MI) or stroke. The medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline information.

The criteria for definite and probable MI were defined according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project [16], which requires evidence from an electrocardiogram (ECG), cardiac enzymes and/or autopsy. Stroke was defined according to the National Survey of Stroke criteria [17], which requires the rapid onset of a constellation of neurological deficits lasting at least 24 h or until death. The strokes were classified as either ischemic stroke (thrombotic or embolic), intracerebral hemorrhage, subarachnoid hemorrhage or undetermined type. A definite stroke was defined by autopsy or on the basis of diagnostic imaging, such as computed tomography or magnetic resonance imaging.

Cases with typical clinical symptoms, detected in the clinical visit during follow-up surveillance, but without informed consent for an in-hospital medical records survey, were defined as possible MI or stroke. Furthermore, to complete the surveillance for fatal MI and stroke, we conducted a systematic search for death certificates. All death certificates in Japan are forwarded to the Ministry of Health, Welfare, and Labor and coded for National Vital Statistics. We classified fatal MI and stroke listed on the death certificate, but not registered on our surveillance system, as possible MI and stroke.

### 2.4. Statistical analysis

Sex-specific analysis was performed. We set the cut-off points for serum LDL-C and non-HDLC according to the quintile ranges. For baseline characteristics, analysis of variance for means or Chi-square tests for proportions were used. The multivariable-adjusted hazard ratio (HR) of LDL-C and non-HDLC for MI or stroke was calculated using proportional hazards model adjusted for age, hypertension, diabetes, HDL-C, body mass index (BMI), smoking (never-smoked; ex-smoker; current smoker) and drinking (never-drank; ex-drinker; regular drinker). Sex-combined analysis with further adjustment for sex was also carried out.

Separate models with LDL-C or non-HDLC levels as ordinal variables (median of LDL-C or non-HDLC quintile) were fitted to the other risk factor adjusted models (test for trend). The differences between the −2 logarithm likelihood (−2 ln [L]) in each lipid added model and the −2 ln [L] in other risk factor adjusted models were calculated. These differences had an approximate $\chi^2$ distribution with 1 d.f. These $\chi^2$ values assess which lipid had the greatest predictive value in other risk factor adjusted models. The ability to predict which people developed cardiovascular disease was also assessed by calculating the area under the receiver-operating characteristic (ROC) curve (AUC). This curve showed the predictive probability of the variables using logistic regression analysis and the same covariates used in the multivariable model of test for trend. Furthermore, the predictive values of the ratio of LDL-C to HDL-C (LDL-C/HDL-C) and the ratio of non-HDLC to HDL-C (non-HDLC/HDL-C) for myocardial infarction (MI) and stroke were also compared.

All confidence intervals were estimated at the 95% level and significance was set at a $P$ value of <0.05. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 15.0J, Tokyo, Japan) was used for all the analyses.

## 3. Results

The mean and standard deviation of serum LDL-C in the baseline survey was 3.23 ± 0.82 mmol/l (124.9 ± 31.7 mg/dl) in men and 3.49 ± 0.90 mmol/l (134.8 ± 34.9 mg/dl) in women. The mean baseline serum non-HDLC was 3.90 ± 0.89 mmol/l (151.1 ± 34.5 mg/dl) in men and 4.01 ± 1.01 mmol/l (155.2 ± 39.1 mg/dl) in women.

Table 1 shows the baseline characteristics of the participants in each LDL-C quintile. In both sexes, there were significant differences in the mean values for age, non-HDLC, HDL-C and BMI. These variables, with the exception of HDL-C, tended to be higher in the higher LDL-C groups. Serum HDL-C levels were lower in the higher LDL-C groups. There was no significant difference in the prevalence of hypertension and diabetes in the quintiles for men, whereas the prevalence of these conditions in women was higher in the higher LDL-C groups. In both sexes, the proportion of current drinkers was lower in the higher LDL-C groups, whereas the proportion of current smokers was highest in the lowest LDL-C group. The relationships between non-HDLC quintiles and the above-mentioned baseline characteristics were almost similar (data not shown in the table).

The total person-years studied was 56,196 (25,420 for men and 30,776 for women), with a mean follow-up period of 11.9 years. During the follow-up period, there were 80 incident cases of MI (41 definite and 39 probable MIs) and 139 of stoke (102 definite and 37

**Table 1**
Sex-specific mean and prevalence of risk characteristics at baseline in an 11.9-year prospective study of 4694 Japanese men and women

| LDL cholesterol quintiles | Q1 | Q2 | Q3 | Q4 | Q5 | *P*-values |
|---|---|---|---|---|---|---|
| Men | | | | | | |
| Numbers | 447 | 435 | 427 | 438 | 422 | |
| LDL cholesterol (Stratum Mean), mmol/l | 2.13 | 2.80 | 3.22 | 3.66 | 4.40 | |
| Age, year | 54.0 (12.7) | 53.8 (12.6) | 52.5 (12.4) | 54.7 (12.1) | 55.6 (11.0) | 0.005 |
| Non-HDL cholesterol, mmol/l | 2.84 (0.52) | 3.44 (0.39) | 3.87 (0.34) | 4.31 (0.32) | 5.13 (0.56) | <0.001 |
| HDL cholesterol, mmol/l | 1.33 (0.39) | 1.29 (0.36) | 1.29 (0.32) | 1.26 (0.30) | 1.21 (0.28) | <0.001 |
| BMI, kg/m$^2$ | 22.1 (2.9) | 22.6 (2.8) | 22.9 (2.8) | 23.2 (2.6) | 23.4 (2.7) | <0.001 |
| Hypertension, % | 29.5 | 27.4 | 30.4 | 31.3 | 33.6 | 0.364 |
| Diabetes, % | 8.1 | 4.6 | 4.4 | 4.6 | 5.9 | 0.091 |
| Drinking | | | | | | |
| Usual/ex-/never-, % | 81.9/2.7/15.4 | 78.2/2.8/19.1 | 79.6/1.6/18.7 | 71.7/5.3/23.1 | 70.4/4.7/24.9 | <0.001 |
| Smoking | | | | | | |
| Current/ex-/never-, % | 59.3/25.5/15.2 | 55.4/26.9/17.7 | 46.6/31.1/22.2 | 46.6/31.1/22.4 | 48.1/31.8/20.1 | 0.002 |
| Women | | | | | | |
| Numbers | 524 | 498 | 513 | 498 | 492 | |
| LDL cholesterol (Stratum Mean), mmol/l | 2.33 | 2.98 | 3.44 | 3.92 | 4.82 | |
| Age, year | 45.5 (11.4) | 49.9 (11.9) | 52.7 (11.3) | 56.3 (10.6) | 57.8 (9.1) | <0.001 |
| Non-HDL cholesterol, mmol/l | 2.77 (0.42) | 3.47 (0.32) | 3.96 (0.31) | 4.50 (0.32) | 5.46 (0.71) | <0.001 |
| HDL cholesterol, mmol/l | 1.54 (0.36) | 1.49 (0.36) | 1.48 (0.35) | 1.45 (0.33) | 1.40 (0.31) | <0.001 |
| BMI, kg/m$^2$ | 21.0 (2.7) | 21.8 (3.2) | 22.3 (3.3) | 22.6 (3.2) | 23.2 (3.3) | <0.001 |
| Hypertension, % | 12.8 | 19.3 | 23.4 | 29.9 | 37.8 | <0.001 |
| Diabetes, % | 1.5 | 2.8 | 3.1 | 4.0 | 4.7 | 0.050 |
| Drinking | | | | | | |
| Usual/ex-/never-, % | 41.8/2.3/55.9 | 36.5/1.0/62.4 | 32.7/1.4/65.9 | 28.3/1.8/69.9 | 29.1/1.6/69.3 | <0.001 |
| Smoking | | | | | | |
| Current/ex-/never-, % | 16.4/4.6/79.0 | 12.7/3.8/83.5 | 9.6/2.1/88.3 | 10.8/3.4/85.7 | 11.6/3.7/84.8 | 0.015 |

HDL means high-density lipoprotein. LDL means low-density lipoprotein. S.D. means standard deviations. Brackets indicate standard deviation. Analysis of variance was used for comparisons of multiple group means and the Chi-square test was used to compare frequencies.

probable strokes), comprised of 23 intracerebral hemorrhages, 85 cerebral infarctions and 31 other types of stroke.

Table 2 shows the number of incident cases and multivariable-adjusted HRs for MI and cerebral infarction stratified by LDL-C quintile. In women, the bottom and second quintiles and the third and fourth quintiles were combined into two categories due to the small number of cardiovascular events. In both sexes, the HR for MI was highest in the top quintile of LDL-C, although the value in women was not statistically significant (HR 3.73; 95% CI 1.25–11.1 for men: HR 1.78; 95% CI 0.66–4.77 for women). In the test for trend, serum LDL-C showed a significant positive association with MI when the data from men and women were combined

**Table 2**
The numbers of cases and multivariable-adjusted HRs and 95% C.I.s for myocardial infarction and cerebral infarction according to serum LDL cholesterol level in an 11.9-year prospective study of 4694 Japanese men and women

| LDL cholesterol quintiles | LDL-C range (mmol/l) | No. of persons | Person-years | Myocardial infarction | | | Cerebral infarction | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | No. of events | HR[a] | 95% C.I. | No. of events | HR[a] | 95% C.I. |
| Men | | | | | | | | | |
| Q1 | <2.54 | 447 | 5,129 | 4 | 1.00 | | 14 | 1.00 | |
| Q2 | 2.54–3.03 | 435 | 5,122 | 15 | 3.56 | 1.18, 10.8 | 9 | 0.61 | 0.26, 1.42 |
| Q3 | 3.04–3.43 | 427 | 4,945 | 9 | 2.60 | 0.80, 8.5 | 15 | 1.31 | 0.63, 2.72 |
| Q4 | 3.44–3.90 | 438 | 5,201 | 10 | 2.25 | 0.70, 7.2 | 13 | 0.90 | 0.42, 1.94 |
| Q5 | 3.91– | 422 | 5,023 | 18 | 3.73 | 1.25, 11.1 | 6 | 0.42 | 0.16, 1.10 |
| | | | | | *P* for trend | 0.08 | | *P* for trend | 0.22 |
| Women | | | | | | | | | |
| Q1 + Q2[b] | <3.21 | 1022 | 12,473 | 6 | 1.00 | | 7 | 1.00 | |
| Q3 + Q4[b] | 3.22–4.22 | 1011 | 12,279 | 5 | 0.45 | 0.14, 1.49 | 11 | 0.82 | 0.31, 2.15 |
| Q5 | 4.23 | 492 | 6,023 | 13 | 1.78 | 0.66, 4.77 | 10 | 1.13 | 0.42, 3.02 |
| | | | | | *P* for trend | 0.14 | | *P* for trend | 0.88 |
| Men and women combined | | | | | | | | | |
| Q1 | | 971 | 11,548 | 7 | 1.00 | | 19 | 1.00 | |
| Q2 | | 933 | 11,176 | 18 | 2.37 | 0.97, 5.61 | 11 | 0.53 | 0.25, 1.12 |
| Q3 | [c] | 940 | 11,102 | 11 | 1.57 | 0.61, 4.08 | 18 | 0.95 | 0.49, 1.82 |
| Q4 | | 936 | 11,323 | 13 | 1.40 | 0.56, 3.55 | 21 | 0.84 | 0.44, 1.59 |
| Q5 | | 914 | 11,046 | 31 | 3.03 | 1.32, 6.96 | 16 | 0.63 | 0.32, 1.24 |
| | | | | | *P* for trend | 0.02 | | *P* for trend | 0.47 |

LDL means low-density lipoprotein.

[a] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, diabetes, HDL cholesterol, cigarette smoking category and alcohol intake category by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.

[b] These groups were combined due to small number of cardiovascular event. The cut-off points were 2.73 between Q1 and Q2, and 3.68 between Q3 and Q4, respectively.

[c] Sex-specific quintiles were used for analysis.

**Table 3**
The numbers of cases and multivariable-adjusted HRs and 95% C.I.s for myocardial infarction and cerebral infarction according to serum non-HDL cholesterol level in an 11.9-year prospective study of 4694 Japanese men and women

| Non-HDL cholesterol quintiles | Non-HDLC range (mmol/l) | No. of persons | Person-years | Myocardial infarction | | | Cerebral infarction | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | No. of events | HR[a] | 95% C.I. | No. of events | HR[a] | 95% C.I. |
| Men | | | | | | | | | |
| Q1 | <3.18 | 445 | 5,123 | 6 | 1.00 | | 11 | 1.00 | |
| Q2 | 3.18–3.68 | 450 | 5,195 | 14 | 2.34 | 0.89, 6.16 | 13 | 1.21 | 0.54, 2.73 |
| Q3 | 3.69–4.12 | 426 | 5,077 | 7 | 1.21 | 0.40, 3.64 | 12 | 1.26 | 0.54, 2.91 |
| Q4 | 4.13–4.63 | 428 | 5,041 | 10 | 1.49 | 0.53, 4.16 | 11 | 0.97 | 0.41, 2.31 |
| Q5 | 4.64 | 420 | 4,982 | 19 | 2.61 | 1.00, 6.80 | 10 | 0.98 | 0.40, 2.40 |
| | | | | | *P* for trend | 0.12 | | *P* for trend | 0.79 |
| Women | | | | | | | | | |
| Q1+Q2[b] | <3.70 | 1043 | 12,821 | 4 | 1.00 | | 7 | 1.00 | |
| Q3+Q4[b] | 3.71–4.87 | 1010 | 12,205 | 7 | 0.76 | 0.21, 2.72 | 11 | 0.67 | |
| Q5 | 4.88 | 472 | 5,750 | 13 | 1.77 | 0.50, 6.25 | 10 | 0.80 | |
| | | | | | *P* for trend | 0.10 | | *P* for trend | |
| Men and women combined | | | | | | | | | |
| Q1 | | 998 | 11,931 | 7 | 1.00 | | 15 | 1.00 | |
| Q2 | | 940 | 11,208 | 17 | 2.35 | 0.97, 5.69 | 16 | 1.03 | 0.50, 2.10 |
| Q3 | [c] | 947 | 11,412 | 11 | 1.38 | 0.53, 3.60 | 14 | 0.83 | 0.40, 1.76 |
| Q4 | | 917 | 10,911 | 13 | 1.40 | 0.55, 3.57 | 20 | 1.03 | 0.51, 2.06 |
| Q5 | | 892 | 10,732 | 32 | 2.97 | 1.26, 6.97 | 20 | 0.99 | 0.48, 2.03 |
| | | | | | *P* for trend | 0.02 | | *P* for trend | 0.96 |

HDL means high-density lipoprotein.

[a] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, hypertension, diabetes, HDL cholesterol, cigarette smoking category and alcohol intake category by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.

[b] These groups were combined due to small number of cardiovascular event. The cut-off points were 3.21 between Q1 and Q2, and 4.26 between Q3 and Q4, respectively.

[c] Sex-specific quintiles were used for analysis.

($P=0.02$). A similar trend was observed when the endpoint was limited to definite MIs by the criteria of the MONICA project ($P=0.01$, data not shown in the table). The incidence for cerebral infarction was not related to LDL-C levels in either sex. The incidences of intra-cerebral hemorrhage, other types of stroke and total stroke were also not associated with LDL-C levels (data not shown in the table).

Table 3 shows the results stratified by non-HDLC. The HR for MI was highest in the top quintile of non-HDLC in both sexes, although in women the value did not reach statistical significance (HR 2.61; 95% CI 1.00–6.8 for men: HR 1.77; 95% CI 0.50–6.25 for women). In men, the HR for MI was highest in the top quintile of non-HDLC (HR 2.61; 95% CI 1.00–6.80). In the test for trend, serum non-HDLC showed a significant positive association with MI when the data of men and women were combined ($P=0.02$). A similar trend was observed when the endpoint was limited to define MIs ($P=0.01$, data not shown in the table). The incidence of cerebral infarction was not associated with non-HDLC levels in either sex. The other types of stroke and total stroke were also not associated with non-HDLC level (data not shown in the table).

To determine the predictive values of LDL-C and non-HDLC, the difference between the −2 ln [L] of model including each lipid and the −2 ln [L] of other variable-adjusted models was calculated. The $\chi^2$ values for LDL-C and non-HDLC were almost the same at 5.71 ($P=0.02$) for LDL-C and 5.49 ($P=0.02$) for non-HDLC. Furthermore, the AUC of the ROC curves based on predictive probability targeting for MI were also estimated. The AUC of LDL-C and non-HDLC were the same at 0.82.

We calculated the hazard ratios of LDL-C/HDL-C and non-HDLC/HDL-C, and compared the predictive values of these for the incidence of MI and stroke. Both ratios were significantly associated with the increased risk for MI but not with any types of stroke. The multivariable HRs of LDL-C/HDL-C and non-HDLC/HDL-C for MI were 1.32 [95% CI, 1.07–1.61] and 1.25 [95% CI, 1.07–1.47], respectively. Furthermore, the $\chi^2$ values between the −2 ln (L) of each lipid added model and non-added model for LDL-C/HDL-C and non-HDLC/HDL-C were almost the same at 7.34 ($P=0.01$) for LDL-C/HDL-C and 7.06 ($P=0.01$) for non-HDLC/HDL-C. The AUC of the ROC curves based on predictive probability were also the same. Apparently, because non-HDLC/HDLC was expressed as [(TC/HDLC) − 1], the HR and predictive value for TC/HDLC were just the same as those of non-HDLC/HDLC.

When the participants were divided in two groups using the median value of serum triglycerides (1.12 mmol/l, 99 mg/dl), the results of all the analyses listed above were similar.

## 4. Discussion

This 11.9-year cohort study of a Japanese urban population showed a positive association between serum LDL-C or non-HDLC levels and increased risk of MI, but not with any type of stroke. Furthermore, we found there was no substantial difference in the predictive value for MI incidence between LDL-C and non-HDLC. To our knowledge, this is the first cohort study in an urban Japanese population on the relationship between serum lipids and cardiovascular events.

The role of LDL-C in the development of atherosclerosis and the beneficial effect of LDL-C lowering therapy are well established, especially in Western populations [1–4] Our study indicated there is also a positive relationship between serum LDL-C and CAD events in community-dwelling Japanese with no history of cardiovascular disease or use of lipid-lowering agents, such as statins. A recent large clinical trial in Japan [18], the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA study), also have shown an 18% reduction in mean LDL-C (from 4.05 mmol/l to 3.31 mmol/l) was associated with a 33% decreased risk for CAD. These results suggested strongly that management of serum LDL-C levels is as effective for reducing CAD in Japan as it is in Western countries.

Non-HDLC levels are thought to be an alternative predictor that can substitute for LDL-C in patients with hypertriglycemia

[3]. Non-HDLC reflects the total cholesterol concentration of all atherogenic lipoproteins. Several previous studies in US communities [6,7,9,19,20] or patients with type 2 diabetes [21,22] showed that the non-HDLC level was a stronger predictor for CAD risk than LDL-C. In the Lipid Research Clinics Program Follow-up Study [6], differences of 0.78 mmol/l (30 mg/dl) in non-HDLC and LDL-C levels corresponded to increases in CVD risk of 19% and 15% in men, and 11% and 8% in women, respectively. In contrast, Chien et al. showed that the hazard ratio of the top quintile and area under the ROC curve for CAD incidence were almost similar for LDL-C and non-HDLC in ethnic Chinese living in Taiwan [8].

Our results are consistent with the Taiwan study described above [8], which to date represents the only report from a non-Western community. As we calculated serum LDL-C levels using the Friedewald formula, our results were not applicable to the population with serum triglyceride levels equal to or greater than 4.5 mmol/l (≥400 mg/dl). However, even if the predictive values of LDL-C and non-HDLC are similar in the Japanese population, non-HDLC may be the more convenient indicator to use for primary prevention in the community. Both TC and HDL-C are included in routine biochemistry measurements because of convenience and low cost, and can be measured directly even in non-fasting serum. Accordingly, non-HDLC may be a good serum marker for risk assessment of CAD in a community-based setting.

In the present study, the positive association between serum lipids levels and MI in women was less evident than that in men. We believe it was mainly due to small number of MI in women. Continued community surveillance in Japan showed that incidence of MI for women was about one third of men [23]. In the present study, incidence of MI for women was only 0.78 per 1000 person-years. Because most MI cases (22 of 24) were post-menopausal women, the low incidence of MI in pre-menopausal women was one reason for sex-difference. However, it was difficult to perform further analysis because of small sample size of MI cases.

Similar to previous studies that have explored the relationship between TC and stroke in Japan [9,24,25], we found no association between LDL-C or non-HDLC levels and stroke events. A large meta-analysis of individual data from 61 prospective studies [26], the majority of which were from the US, European and Japanese populations, showed an absence of an independent positive association between TC or non-HDLC and ischemic and total stroke mortality. Recently, the death probability over a 10-year period due to MI and stroke have been calculated and displayed as color risk score charts by combining 10-year age, systolic blood pressure, smoking, and serum total cholesterol and glucose levels by NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged) Research group [27]. NIPPON DATA Risk chart for MI clearly showed the positive relationship between TC and MI, however, the risk chart for stroke showed the color gradient, which was shown death probability, for stroke was not affected by TC levels.

The lack of a relationship between TC and ischemic stroke in Japanese studies may be due to a lower prevalence of thrombotic type cortical infarctions (large-artery occlusive) than in Western populations [28], a condition that is associated with atherosclerosis secondary to hypercholesterolemia. Furthermore, the Atherosclerosis Risk in Communities (ARIC) Study also indicated that TC was associated with increased risk of non-lacunar, non-embolic stroke (thrombotic type cortical infarction), but not with lacunar or embolic stroke [29]. The effect of LDL-C or non-HDLC on ischemic stroke may be weak in populations with a low prevalence of large-artery occlusive infarctions, such as in Japan. However, a meta-analysis of randomized control trials by statin therapy has indicated a reduction of stroke [30]. Even in Japanese patients with hypercholesterolemia, statin therapy showed a non-significant but inverse association with cerebral infarction [18]. Accordingly, high serum levels of LDLC or non-HDLC should be dealt with caution as a potential risk factor for ischemic stroke.

Previous studies indicated that CAD or MI morality in Japanese people was still lower than in Westerners [9–12]. However, recently, there were evidences that serum levels of TC and LDL-C in Japanese were as high as those reported in the US population [31]. However, CAD mortality has been shown to be higher in large urbanized areas in Japan such as Tokyo and Osaka compared to the rest of Japan [32]. These two cities are among the most urbanized areas in Asia. The present study therefore provides additional evidence supporting the usefulness of LDL-C and non-HDLC as predictors of future risk for MI in screening of the urbanized Japanese population. Although in Asian countries hypertension rather than LDL-C remains the most important manageable cardiovascular risk factor [33], the present study showed that, at least in urbanized areas, lowering of LDL-C levels should also be considered as an important public health issue.

The present study had some limitations. Firstly, the single LDL-C or non-HDLC measurement at the baseline survey may have underestimated the relationship between these lipids and CAD due to regression dilution bias. Secondly, we did not measure serum apolipoprotein B (apoB), which some previous studies have shown as a stronger predictor for CAD than non-HDLC [8,20]. Furthermore, measurement of apoB is not required fasting status and is estimated to be cost-efficient [34]. Further cohort studies with measurement of apoB are needed in Japanese community-dwelling populations. Thirdly, in order to accurately compare the predictive value of non-HDLC and LDL-C, serum levels of LDL-C should be measured by direct measurement of LDL-C, rather than by the Friedewald formula. Exclusion of participants with a high serum triglyceride level (≥400 mg/dl) may reduce the predictive potential of non-HDLC. Finally, the relationship between serum lipids and cerebral infarction warrants further investigation, as we did not evaluate the effect of serum LDL-C and non-HDLC on each subtype of cerebral infarction due to small sample size, especially for thrombotic type cortical infarctions.

In conclusion, higher levels of serum LDL-C and non-HDLC are both associated with an increased risk of MI, but not with cerebral infarction in a Japanese urban population. Although the predictive value of non-HDLC for MI is almost similar to that of LDL-C calculated by the Friedewald formula, non-HDLC may be recommended as an alternative screening marker for primary prevention of CAD in the community, as it is less expensive and more convenient.

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# Risk of Smoking and Metabolic Syndrome for Incidence of Cardiovascular Disease

## —— Comparison of Relative Contribution in Urban Japanese Population: The Suita Study ——

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***Background:*** Risk factor clustering, the so-called metabolic syndrome (MetS), is an important risk factor for cardiovascular disease (CVD). Smoking is also an important CVD risk factor with still a high prevalence. However, few previous studies have compared the risk for CVD or the population-attributable fraction (PAF) of smoking, MetS, and both.

***Methods and Results:*** The present study was an 11.9-year cohort study of 1,822 men and 2,089 women, aged 40–74 years, selected randomly from an urban general population in Japan. MetS was defined according to the National Cholesterol Education Program on Adult Treatment Panel III (NCEP-ATPIII) guideline modified by the Asian criteria for waist circumference. The prevalence of smoking was 49.5% in men and 11.1% in women, and that of MetS was 19.8% and 23.5%, respectively. In men, the multivariate-adjusted hazard ratio for CVD incidence, compared with non-smoking participants without MetS, was 2.07 (1.26–3.40) in those who smoked, 2.09 (1.08–4.04) in those with MetS, and 3.56 (1.89–6.72) in those with both. In men the PAF for CVD incidence was 21.8% because of smoking, 7.5% because of MetS, and 11.9% because of both.

***Conclusions:*** Although countermeasures for MetS are important, smoking should continue to be considered an important public health problem and antismoking campaigns should be promoted, especially for men, to prevent CVD. (*Circ J* 2009; **73:** 2258–2263)

**Key Words:** Cohort; Hazard ratio; Metabolic syndrome; Smoking

Risk factor clustering, the so-called metabolic syndrome (MetS), is an important risk factor for cardiovascular disease (CVD), and previous studies have shown the risk of MetS for CVD in the Japanese population.[1–4] In addition, health guidance for people aged 40–74 years who fulfill the Japanese MetS criteria[5] began in April 2008 and countermeasures for MetS has become a national project.[6]

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However, cigarette smoking is a widely accepted risk factor for CVD,[7–9] and the prevalence of smoking is still high in Japan compared with Western developed countries.[10] Accordingly, in Japan, countermeasures for MetS are being applied with a still high prevalence of smoking, which might be different from the situation in Western developed countries with a lower prevalence of smoking.[10] To improve this situation, it is important to examine and show the combined risk of MetS and smoking, and compare the impact of each risk factor and both for CVD from the viewpoint of the impact not only on the individual but also on the population using indicators such as population-attributable fraction (PAF). In addition, such an assessment could be useful for motivating individuals with MetS, smoking, or both because both MetS and smoking are targets of lifestyle modification. However, few studies have compared the risk of smoking, MetS, and both for CVD.

Our a priori hypothesis was that the coexistence of smoking and MetS worsens the CVD risk, and that the PAF of smoking in Japanese men is larger than that of MetS because of their high prevalence of smoking. To examine this hypothesis, we performed a 11.9 year (mean length) cohort study in an urban general Japanese population to compare the effects of smoking, MetS and both on CVD risk.

## Methods

### Population

The Suita study,[2,11–14] a cohort study of CVD, was established in 1989 in Suita City, Osaka. In that study, 6,485 participants who were randomly selected from the municipal population registry participated in a baseline survey at the National Cardiovascular Center (NCVC) between

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**Table 1. Baseline Characteristics of the Participants According to the Combination of Smoking and MetS**

| | MetS (–) | | MetS (+) | |
|---|---|---|---|---|
| | Non-smoker | Smoker | Non-smoker | Smoker |
| Men | | | | |
| n | 732 | 730 | 189 | 171 |
| Age (years) | 58.9±9.9 | 56.1±9.4 | 59.3±8.4 | 57.4±9.1 |
| Waist (m) | 0.82±0.07 | 0.81±0.07 | 0.89±0.07 | 0.89±0.07 |
| BMI (kg/m$^2$) | 22.7±2.7 | 22.1±2.5 | 24.9±2.5 | 24.8±2.5 |
| Total cholesterol (mmol/L) | 5.26±0.88 | 5.08±0.85 | 5.49±0.88 | 5.44±0.98 |
| Non-HDL-cholesterol (mmol/L) | 3.90±0.88 | 3.79±0.88 | 4.41±0.85 | 4.41±0.98 |
| High blood pressure (%) | 48.6 | 39.3 | 86.8 | 84.8 |
| High triglycerides (%) | 19.3 | 22.5 | 83.1 | 80.7 |
| Low HDL-cholesterol (%) | 13.5 | 19.6 | 63.0 | 69.6 |
| High blood glucose (%) | 9.6 | 10.0 | 47.1 | 42.1 |
| Abdominal obesity (%) | 13.9 | 7.5 | 56.1 | 59.1 |
| Medication | | | | |
| For hypertension (%) | 32.7 | 33.7 | 36.8 | 39.3 |
| For hypercholesterolemia (%) | 1.0 | 0.5 | 4.8 | 4.1 |
| For hypertriglyceridemia (%) | 0.5 | 0.4 | 2.1 | 1.2 |
| For diabetes (%) | 14.9 | 12.9 | 26.9 | 14.3 |
| Smoking | | | | |
| Never (%) | 37.8 | 0.0 | 32.3 | 0.0 |
| Ex (%) | 62.2 | 0.0 | 67.7 | 0.0 |
| Current (%) | 0.0 | 100.0 | 0.0 | 100.0 |
| Alcohol drinking | | | | |
| Never (%) | 20.9 | 19.6 | 20.6 | 22.8 |
| Ex (%) | 4.2 | 2.5 | 5.8 | 3.5 |
| Current (%) | 74.9 | 77.9 | 73.5 | 73.7 |
| Women | | | | |
| n | 1,424 | 174 | 433 | 58 |
| Age (years) | 55.3±9.4 | 52.6±9.1 | 60.3±8.7 | 59.3±8.6 |
| Waist (m) | 0.77±0.09 | 0.75±0.09 | 0.88±0.09 | 0.87±0.09 |
| BMI (kg/m$^2$) | 21.8±2.8 | 21.4±3.0 | 24.8±3.3 | 24.7±3.2 |
| Total cholesterol (mmol/L) | 5.57±0.90 | 5.39±0.98 | 5.93±1.00 | 5.83±0.98 |
| Non-HDL-cholesterol (mmol/L) | 4.02±0.90 | 3.97±1.03 | 4.75±1.01 | 4.77±0.95 |
| High blood pressure (%) | 35.1 | 20.1 | 85.2 | 70.7 |
| High triglycerides (%) | 6.6 | 6.3 | 58.0 | 81.0 |
| Low HDL-cholesterol (%) | 18.3 | 34.5 | 82.0 | 87.9 |
| High blood glucose (%) | 4.3 | 1.7 | 30.5 | 24.1 |
| Abdominal obesity (%) | 30.1 | 27.6 | 86.6 | 79.3 |
| Medication | | | | |
| For hypertension (%) | 33.7 | 17.4 | 43.6 | 44.4 |
| For hypercholesterolemia (%) | 1.6 | 0.0 | 6.5 | 3.4 |
| For hypertriglyceridemia (%) | 0.1 | 0.0 | 1.4 | 1.7 |
| For diabetes (%) | 16.7 | 0.0 | 17.5 | 30.0 |
| Smoking | | | | |
| Never (%) | 97.1 | 0.0 | 94.2 | 0.0 |
| Ex (%) | 2.9 | 0.0 | 5.8 | 0.0 |
| Current (%) | 0.0 | 100.0 | 0.0 | 100.0 |
| Alcohol drinking | | | | |
| Never (%) | 67.4 | 50.6 | 75.5 | 65.5 |
| Ex (%) | 1.0 | 5.7 | 1.6 | 0.0 |
| Current (%) | 31.6 | 43.7 | 22.9 | 34.5 |

Data are value±indicate standard deviation.
MetS=presence of 3 or more of the following: (1) abdominal obesity defined as a waist circumference ≥90 cm in men and ≥80 cm in women; (2) high blood pressure defined as average systolic/diastolic blood pressures of ≥130/85 mmHg and/or current medication for hypertension; (3) high triglycerides defined as serum level ≥1.68 mmol/L; (4) low HDL-cholesterol defined as serum level <1.03 mmol/L in men and <1.29 mmol/L in women; (5) high blood glucose defined as fasting blood glucose ≥6.10 mmol/L and/or current use of insulin or oral medication for diabetes.
MetS, metabolic syndrome; BMI, body mass index; HDL, high-density lipoprotein.

September 1989 and February 1994. Of the 4,285 participants who were aged 40–74 years at baseline, a total of 374 were excluded for the following reasons: past history of CVD (ischemic heart disease and stroke: n=127), non-fasting visit (n=155), and missing information at the time of the baseline survey or lost to follow-up (n=92). The data for the remaining 3,911 participants (1,822 men and 2,089 women) were then analyzed. Informed consent was given by all participants. The present cohort study was approved by the Institutional Review Board of the NCVC.

### Baseline Examination

Well-trained nurses obtained information on smoking (never, ex-, or current smoker), alcohol drinking (never, ex-, or current drinker), and the medical history of each participant. If the participant answered yes to "current smoker", information was obtained for how many cigarettes per day were smoked.

**Table 2. HRs and 95%CIs of Smoking for Incidence of CVD (Stroke+MI), Stroke, Ischemic Stroke, and MI**

| | Never-smoker | Ex-smoker | Current-smoker | |
|---|---|---|---|---|
| | | | ≤20 cigarettes/day | >20 cigarettes/day |
| Men (n) | 338 | 583 | 524 | 373 |
| Person-years | 4,147 | 6,837 | 5,965 | 4,343 |
| CVD (stroke+MI) | | | | |
| Cases (n) | 11 | 29 | 40 | 16 |
| Incidence (/1,000 person-years) | 2.65 | 4.24 | 6.71 | 3.68 |
| Multivariate-adjusted HR (95%CI) | 1.00 | 1.34(0.67–2.69) | 2.65(1.35–5.21) | 2.31(1.06–5.05) |
| Stroke | | | | |
| Cases (n) | 8 | 18 | 30 | 12 |
| Incidence (/1,000 person-years) | 1.93 | 2.63 | 5.03 | 2.76 |
| Multivariate-adjusted HR (95%CI) | 1.00 | 1.07(0.46–2.48) | 2.47(1.12–5.45) | 2.48(1.00–6.20) |
| Ischemic stroke | | | | |
| Cases (n) | 4 | 16 | 24 | 8 |
| Incidence (/1,000 person-years) | 0.96 | 2.34 | 4.02 | 1.84 |
| Multivariate-adjusted HR (95%CI) | 1.00 | 1.94(0.64–5.86) | 4.06(1.40–11.83) | 3.37(1.00–11.41) |
| MI | | | | |
| Cases (n) | 3 | 11 | 10 | 4 |
| Incidence (/1,000 person-years) | 0.72 | 1.61 | 1.68 | 0.92 |
| Multivariate-adjusted HR (95%CI) | 1.00 | 2.21(0.61–8.00) | 2.74(0.80–10.90) | 1.89(0.41–8.70) |
| Women (n) | 1,790 | 67 | 209 | 23 |
| Person-years | 21,881 | 727 | 2,363 | 240 |
| CVD (stroke+MI) | | | | |
| Cases (n) | 45 | 0 | 10 | 1 |
| Incidence (/1,000 person-years) | 0.21 | – | 4.23 | 4.17 |
| Multivariate-adjusted HR (95%CI) | 1.00 | – | 2.70(1.34–5.45) | 2.80(0.36–21.55) |
| Stroke | | | | |
| Cases (n) | 37 | 0 | 5 | 1 |
| Incidence (/1,000 person-years) | 1.69 | – | 2.12 | 4.17 |
| Multivariate-adjusted HR (95%CI) | 1.00 | – | 1.60(0.62–4.16) | 2.70(0.34–21.68) |
| Ischemic stroke | | | | |
| Cases (n) | 19 | 0 | 4 | 1 |
| Incidence (/1,000 person-years) | 0.87 | – | 1.69 | 4.17 |
| Multivariate-adjusted HR (95%CI) | 1.00 | – | 3.00(1.00–8.97) | 7.15(0.84–60.64) |
| MI | | | | |
| Cases (n) | 8 | 0 | 5 | 0 |
| Incidence (/1,000 person-years) | 0.37 | – | 2.12 | – |
| Multivariate-adjusted HR (95%CI) | 1.00 | – | 8.35(2.64–26.48) | – |

Multivariate-adjusted HR (95%CI): age, BMI, systolic blood pressure, blood glucose, non-HDL-cholesterol, glomerular filtration rate, and alcohol drinking were adjusted.
HRs, hazard ratios; CIs, confidence intervals; CVD, cardiovascular disease; MI, myocardial infarction. Other abbreviations see in Table 1.

Well-trained physicians measured blood pressure (BP) 3 times in the right arm using a standard mercury sphygmomanometer while the participant was seated after a 5-min rest. The average of the 2nd and 3rd measurements was used in the analyses. Height in stockings and weight in light clothing were measured. Trained public health nurses or technicians measured waist circumference at the umbilical level while the participant was standing.

Blood samples were collected at the NCVC after the participants had fasted for at least 12h. The samples were centrifuged immediately, and a routine blood examination, which included serum total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), triglycerides and glucose levels, was then carried out. Non-HDLC was calculated by subtracting the HDL from the TC. Serum creatinine (Cre) was measured by the non-compensated kinetic Jaffe method. The glomerular filtration rate (GFR: $ml \cdot min^{-1} \cdot 1.73 m^{-2}$) was calculated using the MDRD equation modified by the Japanese coefficient (0.881): $186 \times (Cre\ (mg/dl))^{-1.154} \times (age\ (years))^{-0.203} \times 0.881 \times (0.742\ if\ female)$.[15,16]

## Definition of MetS

In the present study, MetS was defined using the criteria recommended in the National Cholesterol Education Program on Adult Treatment Panel III guideline with a modification (modified NCEP-ATP III criteria).[17,18] Specifically, abdominal obesity was defined as a waist circumference ≥90cm in men and ≥80cm in women according to the International Obesity Task Force central obesity criteria for Asia.[17] High BP was defined as average systolic/diastolic BPs ≥130/85mmHg and/or current medication for hypertension. High triglyceride was defined as a serum level ≥1.68mmol/L. Low HDLC was defined as a serum level <1.03mmol/L in men and <1.29mmol/L in women. High blood glucose was defined as fasting blood glucose (FBG) ≥6.10mmol/L and/or current use of insulin or oral medication for diabetes. MetS was defined as the presence of 3 or more of these components.

## Follow-up and Endpoints

The method of follow-up has been described elsewhere.[2,11–14] Briefly, the participants were followed until December 31, 2005. The first step in the survey involved checking the health status of all participants by repeat visits to NCVC every 2 years and yearly questionnaires conducted by mail or telephone interview. The in-hospital medical records of the participants who were suspected of having had a myocardial infarction (MI) or stroke were reviewed

**Table 3. Risk of Smoking and MetS for CVD (Stroke+MI)**

| | MetS (−) | | MetS (+) | |
|---|---|---|---|---|
| | Non-smoker | Smoker | Non-smoker | Smoker |
| Men | | | | |
| n | 732 | 730 | 189 | 171 |
| Person-years | 8,721 | 8,506 | 2,263 | 1,835 |
| CVD (stroke+MI) cases (n) | 26 | 41 | 14 | 16 |
| CVD incidence (/1,000 person-years) | 2.98 | 4.82 | 6.19 | 8.72 |
| Multivariate-adjusted HR (95%CI)† | Reference | 2.03(1.24–3.33) | 2.11(1.10–4.04) | 3.39(1.81–6.33) |
| Multivariate-adjusted HR (95%CI)‡ | Reference | 2.07(1.26–3.40) | 2.09(1.08–4.04) | 3.56(1.89–6.72) |
| PAF | | 21.8 | 7.5 | 11.9 |
| Women | | | | |
| n | 1,424 | 174 | 433 | 58 |
| Person-years | 17,684 | 2,027 | 4,925 | 577 |
| CVD (stroke+MI) cases (n) | 23 | 6 | 22 | 5 |
| CVD incidence (/1,000 person-years) | 1.30 | 2.96 | 4.47 | 8.67 |
| Multivariate-adjusted HR (95%CI)† | Reference | 2.64(1.07–6.51) | 2.58(1.42–4.69) | 5.40(2.04–14.25) |
| Multivariate-adjusted HR (95%CI)‡ | Reference | 2.67(1.07–6.65) | 2.33(1.25–4.34) | 4.84(1.81–12.97) |
| PAF | | 6.7 | 22.4 | 7.1 |

Multivariate-adjusted HR (95%CI): †adjusted for age.
Multivariate-adjusted HR (95%CI): ‡adjusted for age, alcohol drinking (never-, ex-, current-), glomerular filtration rate and non-HDL-cholesterol.
PAF, population attributable fraction. Other abbreviations see in Tables 1,2.

by registered hospital physicians or research physicians who were unaware of the baseline information.

The criteria for definite and probable MI were defined according to the criteria of the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) project,[19] which requires evidence from an ECG, cardiac enzymes, and/or autopsy. Stroke was defined according to the National Survey of Stroke criteria,[20] which require rapid onset of a constellation of neurological deficits lasting at least 24h or until death. Strokes were classified as ischemic stroke (thrombotic or embolic), intracerebral hemorrhage, subarachnoid hemorrhage, or undetermined type. A definite stroke was defined by autopsy or diagnostic imaging, such as computed tomography or magnetic resonance imaging. In the present study, cases of definite MI or stroke were used in the analysis.

### Statistical Analysis

To compare baseline risk characteristics among the 4 groups classified by the combination of MetS and smoking status, analysis of variance was used for continuous variables, and the chi-squared test was used for dichotomous variables. In this analysis, ex-smoker and never-smoker were classified as non-smokers.

Sex-specific analyses were performed. First, the Cox proportional hazards model was used to estimate the hazard ratios (HR) of smoking status for the incidence of CVD (stroke+MI) and its subtypes. Smoking status was classified as never-, ex-, or current smoker (≤20 cigarettes/day and >20 cigarettes/day). In this analysis, age, body mass index (BMI), systolic BP, FBG, non-HDLC,[11] GFR, and alcohol drinking (never-, ex-, and current drinker) were included as confounding factors.

Second, the source population was divided into 4 groups according to the combination of smoking and the presence of MetS. In this analysis, ex-smoker and never-smoker were also classified as non-smokers. The 2 models were used for estimating the HRs of the combinations for CVD incidence. To adjust for the confounding factors, only age was included in model 1, and alcohol drinking (never, ex-, and current drinker), GFR and non-HDLC were also included in model 2. To express the impact of smoking on CVD incidence in the participants, the PAF (%) was estimated as $Pe\times(HR-1)/HR$, in which Pe is the proportion of incident cases in each category.[21]

All statistical analyses were performed using SPSS statistical software, version 15.0 J (SPSS, Tokyo, Japan). $P<0.05$ (2-tailed) was considered statistically significant.

## Results

### Baseline Characteristics

Among the participants, 901 of the 1,822 men and 232 of 2,089 women were current smokers (smoking rate: men, 49.5%; women, 11.1%). Similarly, 360 men and 491 women had MetS (prevalence: men, 19.8%; women, 23.5%). **Table 1** summarizes the baseline characteristics of the participants classified into 4 groups according to the combination of current smoking and MetS by sex. All variables, except for alcohol drinking in men, were significantly different among the 4 groups.

### Risk of Smoking for CVD Incidence

In the present study, the mean follow-up period was 11.9 years, and 42 definite cases of MI and 111 of definite stroke occurred.

**Table 2** shows the multivariate-adjusted HRs and 95% confidence intervals (CI) of smoking status for the incidence of CVD and its subtypes. In men, the HR of current smokers who were smoking ≤20 cigarettes/day compared with never smokers was 2.65 (95%CI 1.35–5.21) for CVD, 2.47 (95%CI 1.12–5.45) for stroke, 4.06 (95%CI 1.40–11.83) for ischemic stroke, and 2.74 (95%CI 0.80–10.90) for MI. Similarly in women, the HR was 2.70 (95%CI 1.34–5.45) for CVD, 1.60 (95%CI 0.62–4.16) for stroke, 3.00 (95%CI 1.00–8.97) for ischemic stroke, and 8.35 (95%CI 2.64–26.48) for MI. Among the participants who were smoking >20 cigarettes/day, the HRs for CVD incidence were similar to those who were smoking ≤20 cigarettes/day, although in both men and women most of them did not reach to statistical significance because of the small sample size.

Among the ex-smokers, the HR was 1.34 (95%CI 0.67–

2.69) for CVD incidence, 1.07 (95%CI 0.46–2.48) for stroke, 1.94 (95%CI 0.64–5.86) for ischemic stroke, and 2.21 (95%CI 0.61–8.00) for MI in men. In women, there was no case of CVD among ex-smokers.

**Risk of Smoking and MetS for CVD Incidence**

**Table 3** shows the multivariate-adjusted HRs of the combination of smoking and MetS for CVD incidence.

In men, the multivariate-adjusted HRs were 2.07 (95%CI 1.26–3.40) for participants with smoking without MetS, 2.09 (95%CI 1.08–4.04) for those with MetS without smoking, and 3.56 (95%CI 1.89–6.72) for those with both, compared with those both smoking and MetS. In women, the multivariate-adjusted HRs were 2.67 (95%CI 1.07–6.65) for participants with smoking without MetS, 2.33 (95%CI 1.25–4.34) for those with MetS without smoking, and 4.84 (95%CI 1.81–12.97) for those with both, compared with those without both smoking and MetS. When we excluded the ex-smokers among women in this analysis, the HRs were almost similar to the results shown in **Table 3**. And these results were not substantially affected when TC instead of non-HDLC was included as a confounding factor in the Cox proportional hazard models.

In men the PAF for CVD incidence was 21.8% because of smoking, 7.5% because of MetS, and 11.9% because of both. In women, the respective PAFs were 6.7%, 22.4%, and 7.1%.

## Discussion

To our knowledge, this is the first report of a comparison of the CVD risk of smoking, MetS, and both. The magnitude of the HR of smoking or MetS was almost equal. As expected, the risk for the participants with both was the highest. The PAF for CVD incidence among men with smoking alone was much higher than that among those with MetS alone. In women, the PAF among those with MetS was higher than that among those with smoking.

Furthermore, this is also the first report to show the risk of smoking for CVD in an urban area of Japan. In the present study, the prevalence of smoking was 49.5% in men and 11.1% in women. Compared with the data from the National Health and Nutrition Survey conducted in 1989 (men aged 40–69 years in 1989, 50.4–59.5%; women aged 40–69 years in 1988, 6.8–10.6%)[22] and several large collaborative cohort studies in Japan,[8,9,23,24] the prevalence of smoking in the present study was lower in men and higher in women, but is most consistent with the current Japanese prevalence of smoking (men: 39.9%; women: 10.0%). The present study might reflect the prevalence of smoking in urban Japanese communities around the 1990s. In addition, the high smoking prevalence in women and low prevalence in men in the present study is consistent with that in most of the Asia-Pacific region.

Our study showed that smoking is a prominent risk factor for CVD in an urban Japanese cohort, as shown in previous studies in Japanese rural populations.[9,23,24] Similarly, as previously reported,[1,25–27] MetS was a risk factor for CVD in our cohort.[2] The association between MetS and CVD has been reported in several Japanese cohort studies; however, the number of participants was fewer than in the present study,[1] or non-fasting blood samples and BMI were used instead of waist circumference for the analysis.[25] These points are another important strength of our study.

MetS has been reported as associated with high percent plaque volume and abnormal plaque quality in coronary arteries,[28] and chronic subclinical inflammation.[29] As for smoking, Howard et al reported that smoking is associated with progression of an index of atherosclerosis expressed as the intima–medial thickness of the carotid artery.[30] Antoniades et al also stated that smoking induces both functional and structural abnormalities in the vascular wall, by mechanisms involving endothelial dysfunction and impairment of vascular smooth muscle cells in the human arterial tree.[31] They also stated that smoking must be approached within the context of the overall lifestyle: smoking coexists with a pro-atherogenic metabolic profile.[31] The reason for the elevated CVD risk among the present participants with both MetS and smoking is unclear, but the concurrent effect on plaque formation by MetS and smoking, and the additional abnormality in function of vascular smooth muscle cells because of smoking, might be associated with the highest CVD risk among the participants with both risk factors in the present study. Individuals with both smoking and MetS are inevitably in the highest risk group for CVD and should be targeted for intervention.

We compared the HRs of these important CVD risk factors, and the HRs of smoking or MetS for CVD incidence were almost consistent. Accordingly, we calculated the PAF, which shows the impact on CVD incidence. As the result, the PAF of smoking was higher than that of MetS in men, and that of MetS was higher than that of smoking in women, a result that may reflect the higher smoking rate in men. Our study results offer a simple key to solving the problem of "which risk factor should we intervene on first for the population to improve their health outcome". Recently, the smoking rate has been decreasing in Japanese men; however, compared with the United States for example,[10] it remains still high. As well as countermeasures against MetS, we need to continue considering smoking as an important public health problem and promoting antismoking campaigns in Japan.

In Western developed countries such as the United States, evaluating the risk of MetS under a high prevalence of smoking is difficult because the prevalence of smoking is much lower[10] than in Japan. Although the data of the present study are limited to 1 city in Japan, it might offer evidence of the risk of MetS under a high prevalence of smoking.

There has been controversy about defining the optimal diagnostic criteria for MetS. We have already compared the predictive value between the Japanese criteria and the modified NCEP-ATPIII criteria.[2] The results suggested that the modified NCEP-ATPIII criteria are suitable for predicting CVD in the Japanese community setting, as well as in the Hisayama study.[1] Accordingly, in the present study MetS was defined using the modified NCEP-ATPIII criteria[17,18] Some investigators consider that MetS is an adipose tissue disease different from obesity. If it is an adipose tissue disease, it would be characterized by inflammation detected through high-sensitivity C-reactive protein (hs-CRP) and insulin resistance, reflecting histological changes in adipose tissue.[32] Thus, inflammation-related factors such as hs-CRP might be a candidate for 1 of the components of MetS.[33] Furthermore, according to the Japanese MetS criteria, the prevalence of MetS tends to be very low in women because obesity is a required component and the definition of obesity is waist circumference ≥90 cm. In addition, because some previous studies showed that the prevalence of non-obese individuals with several metabolic risk factors is high

and their CVD risk is also high, the simple exclusion of non-obese participants from the diagnosis of MetS may overlook their potential risk for CVD.[25–27] We might misclassify participants with a high risk for CVD if we adopt the Japanese MetS criteria.

## Study Limitations

First, we could not assess the risk of smoking on the incidence of hemorrhagic stroke because of the small number of cases. Second, the measurement of single MetS components and the questionnaire for smoking in the baseline survey may have underestimated the relationship between these risk factors and CVD because of a regression dilution bias.

In conclusion, smoking is still an important risk factor for CVD in urban areas of Japan, and the combination of smoking and MetS worsens the risk for CVD. Lifestyle modification for not only MetS but also smoking continues to be important in populations with a high PAF for CVD because of a high prevalence of smoking.

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## Disclosure

None.

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# 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

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***Background and Purpose***—Chronic kidney disease (CKD) is increasingly recognized as an independent risk factor for stroke and myocardial infarction (MI). Few studies, however, have examined the relationship between blood pressure (BP) category and these diseases in subjects with and without CKD.

***Methods***—We studied 5494 Japanese individuals (ages 30 to 79, without stroke or MI at baseline) who completed a baseline survey and received follow-up through December 2005. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease study equation modified by the Japanese coefficient. CKD was defined as an estimated GFR <60 mL/min/1.73m$^2$. BP categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

***Results***—In 64 395 person-years of follow-up, we documented 346 incidences of cardiovascular diseases (CVD; 213 strokes and 133 MI events). Compared with the GFR (≥90 mL/min/1.73m$^2$) group, the hazard ratios (95% confidential intervals) for stroke were 1.9 (1.3 to 3.0) in the GFR 50 to 59 mL/min/1.73m$^2$ group and 2.2 (1.2 to 4.1) in the GFR <50 mL/min/1.73m$^2$ group. Results for cerebral infarction were similar. Compared with the optimal BP subjects without CKD, the normal BP, high-normal BP, and hypertensive subjects without CKD showed increased risks of CVD and stroke; however the impact of each BP category on CVD (*P* for interaction: 0.04 in men, 0.49 in women) and stroke (0.03 in men, 0.90 in women) was more evident in men with CKD.

***Conclusions***—CKD may increase the association of BP and CVD in a Japanese urban population. (***Stroke.* 2009;40:2674-2679.)**

**Key Words:** chronic kidney disease ■ blood pressure category ■ stroke ■ myocardial infarction ■ epidemiology ■ prospective studies ■ general population

Recently, chronic kidney disease (CKD) has become a major public health problem and a risk factor for all-causes mortality, stroke, and myocardial infarction (MI).[1] In end-stage renal disease, the cardiovascular disease (CVD) mortality rate is more than 10 times as high as that in the general population.[2] In asymptomatic general populations or outpatients, a severely or moderately decreased glomerular filtration rate (GFR) has been shown by most but not all studies to be an independent risk factor for stroke and MI.[1] However, in low-risk or general populations, the relationship between levels of kidney function and clinical outcomes has not been as clear. Some studies have demonstrated no association between CKD and CVD,[3,4] whereas others have shown CKD as an independent risk factor for CVD.[5–8] These inconsistencies may be attributable to differences between the selected study populations as well as the severity of the CKD.

The frequency of hypertension is relatively higher in Japanese than in Western countries.[9] Hypertension is one of the major risk factors for both CVD and CKD. Recently, a larger prospective study has indicated that CKD increased the association between blood pressure (BP) categories and CVD, although the relevant data were gathered from 10 rural areas with different methods

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for the measurement of creatinine.[10] A few studies in general population have demonstrated a stronger association between BP and CVD in subjects with CKD.[5,10] We examined the association between BP category and incidence of stroke and MI subjects with and without CKD in a Japanese urban population.

## Methods

### Study Subjects

Suita city is located adjacent to Osaka city, which is the second largest metropolitan area in Japan. The Suita Study,[11–13] an epidemiological study of cerebrovascular and cardiovascular diseases, was based on a random sampling of 12 200 Japanese urban residents. As a baseline, participants (aged 30 to 79 years) were randomly selected from the municipality population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6485 people underwent regular health checkups between September 1989 and March 1994.

Cohort members in the study population were excluded from these analyses if they had a past or present history of CVD at baseline (n=208), were missing data (n=170), attended health checkups after April 1994 (n=79), or failed to complete the follow-up health surveys or questionnaires after the baseline examination (n=534). After applying these exclusions, a total of 5494 participants aged 30 to 79 years old were selected. Informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the National Cardiovascular Center.

### Measurement of Blood Pressure and Covariates

Well-trained physicians measured BP 3 times using a mercury column sphygmomanometer, an appropriate-size cuff, and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. First, systolic blood pressure (SBP) was measured for the purpose of obtaining approximate SBP levels. SBP and diastolic blood pressures (DBP) were taken as the average of the second and third measurements, which were recorded more than 1 minute apart.

At the time of the baseline examination, subjects were classified into 1 of the 5 BP categories based on the European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 criteria[14]: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg), high-normal BP (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg), and hypertensive (SBP ≥140 mm Hg or DBP ≥90 mm Hg). Antihypertensive drug users were classified according to their BP levels at the baseline survey. If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the two BP categories.

At the baseline examination, we performed routine blood tests that included serum total cholesterol, HDL cholesterol, and glucose levels. Physicians or nurses administered questionnaires covering personal habits and present illness. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Hypercholesterolemia was defined as total cholesterol levels ≥5.7 mmol/L or current use of antihyperlipidemic medications. Diabetes was defined as a fasting plasma glucose level ≥7.0 mmol/L, a nonfasting plasma glucose level ≥11.0 mmol/L, or current use of antidiabetic medications.

### Definition of CKD

Serum creatinine (Cre) was measured by noncompensated kinetic Jaffé methods. The glomerular filtration rate (GFR) of each participant was calculated from the Cre value and the age, using the MDRD equation modified by the Japanese coefficient (0.881), as follows[15]:

$$\text{GFR (ml/min/1.73 m}^2\text{)} = 0.881 \times 186 \times \text{age}^{-0.203} \times \text{Cre}^{-1.154} \text{ (for men)}$$

$$\text{and GFR (ml/min/1.73 m}^2\text{)} = 0.881 \times 186 \times \text{age}^{-0.203} \times \text{Cre}^{-1.154} \times 0.742 \text{ (for women).}$$

CKD was defined as an estimated GFR <60 mL/min/1.73m$^2$.

### Confirmation of Stroke and MI and End Point Determination

The confirmation of stroke and MI in the Suita Study has been described elsewhere.[11–13] In brief, the 5 hospitals in this area, where acute stroke and MI patients were admitted, were all capable of performing computed tomographic scans or MRI. Medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline data. Strokes were defined according to the U.S. National Survey of Stroke criteria.[16] For each stroke subtype (ie, cerebral infarction [thrombotic or embolic infarction], intracerebral hemorrhage, and subarachnoid hemorrhage), a definite diagnosis was established based on examination of computed tomographic scans, magnetic resonance images, or autopsies. Definite and probable MIs were defined according to the criteria set out by the MONICA project.[17] Sudden deaths of unknown origin were deaths that occurred within 24 hours from the onset of symptoms, and were also classified as MI. In this study CVD was defined as stroke or MI.

To detect MI and stroke occurrences, each participant's health status was checked at clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed for all participants. In addition, to complete our surveillance for fatal strokes and MIs, we conducted a systematic search for death certificates. All the data (health check-ups, questionnaires, and death certificates) were checked against medical records to confirm the incidence of CVD. We identified possible strokes or MIs using data from (1) the health examination and questionnaires from the stroke and MI registries without informed consent for medical records survey; and (2) death certificates bearing a diagnosis of probable stroke or MI without registration of CVD incidence.

The end points of the current follow-up study were (1) date of the first MI or stroke event (2); date of death (3); date of leaving Suita; and (4) December 31, 2005 (censored).

### Statistical Analysis

Analyses of variances and $\chi^2$ tests were used to compare mean values and frequencies. The Cox proportional-hazard ratios (HRs) were fitted to the GFR categories and CKD after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors at the baseline survey: namely, present illness of hypertension, hypercholesterolemia and diabetes, smoking status (never, quit, and current smoker), and drinking status (never, quit, and current drinker). The Cox proportional HRs were fitted to the combination of the BP categories and CKD (positive or negative) after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors including an interactive term for CKD and BP categories. The fit of the proportional hazards model was evaluated by examining discrete regression models and by permitting the proportionality assumption to vary with time, and assessments of nonlinearity involving associations with blood pressure and GFR categories were made. The probability values for the model of interaction between CVD incidence and log (person year) were 0.38 in men and 0.81 in women. Proportionality was also checked by log-log survival plot.

To express the impact of CKD on CVD occurrence in the participants, we estimated the population attributable fraction (PAF, %). PAF was estimated as follows:

$$Pe \times (HR-1)/HR,$$

in which $Pe$ is the proportion of incident cases in CKD, and $HR$ is the multiple-adjusted hazard ratio.[18] All statistical analyses were conducted using the SAS statistical package software (release version 8.2, SAS Institute Inc).

## Results

Figure 1 shows that the frequency of CKD increases with age in both men and women. At the baseline survey, both men and women with CKD (8.9% for men and 11.3% for women)

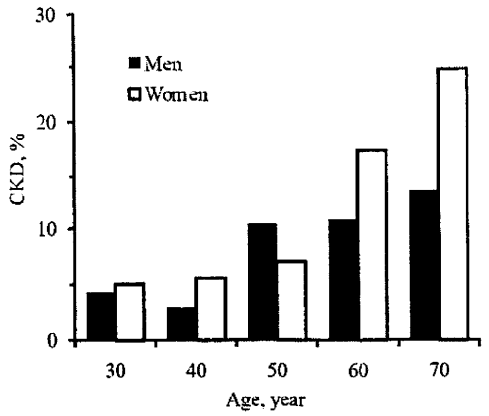


**Figure 1.** Frequencies of CKD according to sex and age.

were older, had higher prevalence of hypertension and hypercholesterolemia, and had a lower frequency of current drinking than those without CKD (Table 1).

During an average 11.7-year follow-up period, we documented 213 strokes and 133 MIs. In men and women combined, compared with subjects for GFR ≥90 mL/min/1.73m$^2$ the multivariable HRs (95% confidence intervals; CIs) for CVD incidence were 1.75 (1.22 to 2.50) in GFR=50 to 59 mL/min/1.73m$^2$ and 2.48 (1.56 to 3.94) in <50 mL/min/1.73m$^2$ (Table 2). In addition, the risks of CVD for each GFR category in men and women separately were similar to the risks for all participants. The multivariable HR (95% CIs) of CVD incidence for CKD was 1.70 (1.30 to 2.23) in all subjects (data not shown).

In Table 3, the multivariable HRs (95% CIs) for strokes were 1.94 (1.26 to 2.98) in the GFR=50 to 59 mL/min/1.73m$^2$ and 2.19 (1.18 to 4.06) in the GFR <50 mL/min/1.73m$^2$ compared with subjects for GFR ≥90 mL/min/1.73m$^2$ Results for cerebral infarction were similar to strokes. Age-adjusted HRs (95% CIs) for intracerebral hemorrhage were 1.93 (0.77 to 4.85) in the GFR=50 to 59 mL/min/1.73m$^2$ and 2.52 (0.72 to 8.80) in the GFR <50 mL/min/1.73m$^2$ (supplemental Table I, available online at http://stroke.ahajournals.org).

In Figure 2, compared with the optimal BP subjects without CKD, the normal BP, high-normal BP, and hypertensive subjects without CKD showed increased risks of CVD, whereas the impact of each BP category on CVD was more evident in subjects with CKD (probability values for interaction between CKD and BP category were 0.04 in men, 0.49 in women, and 0.06 in all subjects). Results of stroke were similar (probability values for the interaction were 0.03 in men and 0.90 in women, data not shown). Supplemental Table II shows the hazard ratios for the association between 10 mm Hg of SBP and the risk of CVD in subjects with or without CKD.

Using the HRs, we estimated the population attributable fraction of CVD to exposure for CKD at baseline by sex. We found that 8.3% in men and 17.6% in men with CVD incidences could be described as excessive incidence attributable to CKD.

## Discussion

In this cohort study of a general urban Japanese population, CKD was a risk factor for CVD and its subtypes. A stronger association between BP and the incidence of CVD was

**Table 1. Baseline Characteristics of Study Subjects According to Chronic Kidney Disease**

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Variables | CKD (−) | CKD (+) | *P* Value | CKD (−) | CKD (+) | *P* Value |
| No. of subjects | 2341 | 229 | | 2593 | 331 | |
| Age at baseline, y | 55±13 | 61±12 | <0.001 | 53±13 | 62±12 | <0.001 |
| Body mass index, kg/m$^2$ | 22±3 | 23±3 | <0.001 | 22±3 | 22±3 | 0.332 |
| Blood pressure category, % | | | 0.005 | | | <0.001 |
| Optimal | 31.7 | 24.0 | | 43.9 | 27.2 | |
| Normal | 19.2 | 14.4 | | 16.6 | 15.4 | |
| High-normal blood pressure | 16.2 | 20.5 | | 14.0 | 14.8 | |
| Hypertension | 32.9 | 41.1 | | 25.5 | 42.6 | |
| Present illness, %* | | | | | | |
| Hypercholesterolemia | 28.1 | 35.8 | 0.014 | 40.7 | 54.7 | <0.001 |
| Diabetes | 6.1 | 6.6 | 0.791 | 3.2 | 5.4 | 0.036 |
| Smoking status, % | | | 0.007 | | | 0.713 |
| Current | 51 | 42 | | 12 | 12 | |
| Quit | 30 | 40 | | 4 | 4 | |
| Never | 19 | 18 | | 84 | 83 | |
| Drinking status, % | | | 0.024 | | | 0.017 |
| Current | 76 | 68 | | 34 | 26 | |
| Quit | 3 | 6 | | 2 | 3 | |
| Never | 21 | 26 | | 65 | 71 | |

*Hypercholesterolemia; antilipidemic drug use or total cholesterol ≥5.7 mmol/L (220 mg/dl), diabetes; antihyperglycemic drug use or fasting blood sugar ≥7.0 mmol/L (126 mg/dl).

Plus–minus values are means±SD.

**Table 2. Age and Multivariable Adjusted Hazard Ratios (95% CIs) for Incidence of Cardiovascular Disease† According to Category of Glomerular Filtration Rate by Sex**

| | Glomerular Filtration Rate, ml/min/1.73m$^2$ | | | | |
|---|---|---|---|---|---|
| Variables | ≥90 | 60 to 89 | 50 to 59 | <50 | *P* for Trend |
| Men and Women | | | | | |
| Cases, n | 94 | 176 | 51 | 25 | |
| Person-years | 28 736 | 29 336 | 4764 | 1558 | |
| Age-adjusted | 1 | 1.22 (0.94–1.58) | 1.71 (1.20–2.42) | 2.49 (1.59–3.90) | <0.001 |
| Multivariable adjusted* | 1 | 1.21 (0.93–1.58) | 1.75 (1.22–2.50) | 2.48 (1.56–3.94) | <0.001 |
| Men | | | | | |
| Cases, n | 50 | 124 | 24 | 11 | |
| Person-years | 12 092 | 14 835 | 1928 | 522 | |
| Age-adjusted | 1 | 1.20 (0.85–1.70) | 1.63 (1.00–2.68) | 2.17 (1.11–4.23) | 0.008 |
| Multivariable adjusted* | 1 | 1.21 (0.85–1.70) | 1.78 (1.08–2.94) | 2.38 (1.21–4.68) | 0.004 |
| Women | | | | | |
| Cases, n | 44 | 52 | 27 | 14 | |
| Person-years | 16 644 | 14 502 | 2836 | 1036 | |
| Age-adjusted | 1 | 1.22 (0.81–1.83) | 1.79 (1.09–2.92) | 2.81 (1.53–5.18) | <0.001 |
| Multivariable adjusted* | 1 | 1.21 (0.80–1.84) | 1.76 (1.05–2.93) | 2.31 (1.20–4.43) | 0.002 |

*Multivariable adjusted for age, BMI, smoking, drinking, and present illness (hypertension, diabetes, and hypercholesterolemia).
†Cardiovascular disease includes both stroke and MI.

observed in the presence of CKD. Furthermore, we found that 8% in men and 18% in women of CVD incidence may be derived from CKD cases.

Go et al reported that both severe and moderate renal diseases were risk factors for CVD incidence.[6] A pooled analysis of community-based studies demonstrated that CKD is an independent risk factor for the composite of all-cause mortality in blacks and whites and CVD incidence in blacks.[5] In contrast, NHANES I did not provide relationships between mortality and moderately higher serum creatinine levels.[4] The Framingham Heart Study and Offspring cohorts have shown no significant association between the presence of kidney disease and CVD incidence.[3]

The results of our study are essentially compatible with previous cohort studies in Japan. The Hisayama study demonstrated that CKD was a risk factor for incidence of coronary heart disease in men and ischemic stroke in women.[8] The Ohasama study indicated that decreased kidney function increased the risk of first symptomatic stroke events.[19] This study used creatinine clearance rather than estimated GFR. Irie et al showed that subjects with GFR <60 had a higher risk of CVD mortality[7] but did not examine the risk of GFR 50 to 59 mL/min/1.73m$^2$ The NIPPON DATA 90 indicated that CKD was an independent risk factor for cardiovascular death in a community-dwelling Japanese population.[20] The end point of these studies was also mortality. Ninomiya et al

**Table 3. Age-Sex and Multivariable Adjusted Hazard Ratios (95% CIs) for Incidence of All Strokes, Cerebral Infarction, and Myocardial Infarction According to Category of Glomerular Filtration Rate**

| | Glomerular Filtration Rate, ml/min/1.73m$^2$ | | | | |
|---|---|---|---|---|---|
| Variables | ≥90 | 60 to 89 | 50 to 59 | <50 | *P* for Trend |
| Person-years | 28 258 | 28 690 | 4528 | 1446 | |
| All strokes | | | | | |
| Cases, n | 65 | 99 | 36 | 13 | |
| Age and sex adjusted | 1 | 1.02 (0.73–1.41) | 1.78 (1.17–2.70) | 1.93 (1.05–3.54) | 0.004 |
| Multivariable adjusted* | 1 | 1.04 (0.74–1.45) | 1.94 (1.26–2.98) | 2.19 (1.18–4.06) | <0.001 |
| Cerebral infarction | | | | | |
| Cases, n | 42 | 66 | 24 | 9 | |
| Age and sex adjusted | 1 | 0.99 (0.66–1.49) | 1.72 (1.03–4.19) | 2.01 (0.97–4.19) | 0.020 |
| Multivariable adjusted* | 1 | 0.98 (0.65–1.49) | 1.81 (1.07–3.07) | 2.26 (1.07–4.78) | 0.008 |
| Myocardial infarction | | | | | |
| Cases, n | 29 | 77 | 15 | 12 | |
| Age and sex adjusted | 1 | 1.68 (1.08–2.61) | 1.64 (0.87–3.09) | 4.26 (2.14–8.45) | <0.001 |
| Multivariable adjusted* | 1 | 1.60 (1.03–2.49) | 1.51 (0.80–2.88) | 3.56 (1.73–7.30) | 0.002 |

*Multivariable adjusted for age, sex, BMI, smoking, drinking, and present illness (hypertension, diabetes, and hypercholesterolemia).

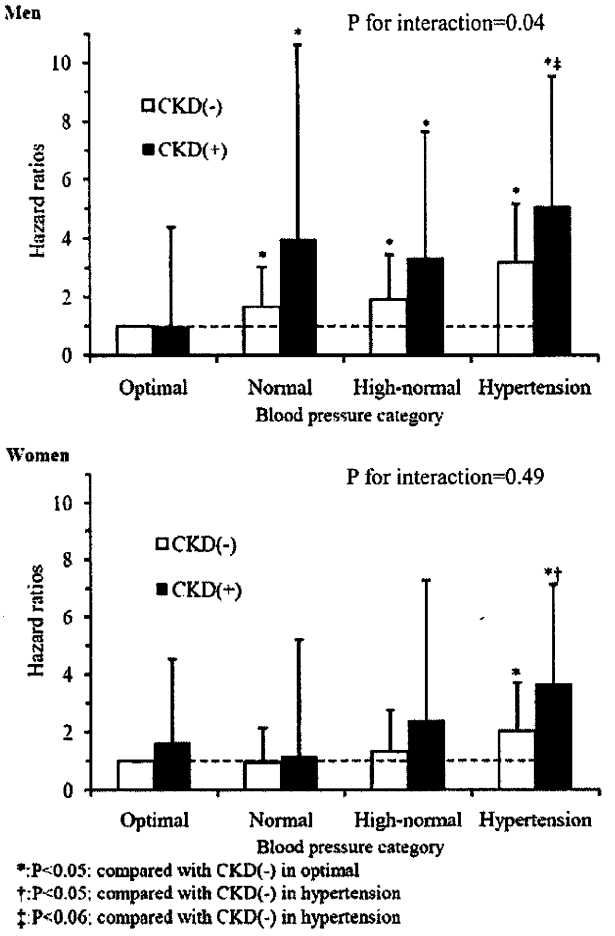


**Figure 2.** The combination of CKD and BP categories on multivariable hazard ratios for CVD. Data for men and women are presented separately. Multivariable analyses are adjusted age in 5-year increments as stratified variables and other potential confounding factors of hypercholesterolemia, diabetes, and smoking and drinking status.

has recently reported that CKD was risk factors for CVD and stroke in women and that CKD increased the association between BP category and CVD in all subjects from 10 combined different cohort studies using different methods of creatinine measurement.[10] All of our samples were measured using the same analyzer at one laboratory.

Compared with the previous studies, our study has several methodological strengths. First, we could perform subanalysis by age and CVD subtype, because we evaluated a large cohort of participants. Second, each participant's health status was checked during a clinical visit at the National Cardiovascular Center every 2 years. In addition, each year, a health questionnaire was given to each participant via mail or telephone. We could evaluate the registry of CVD incidence with the data obtained from clinical visits, annual questionnaires, or death certificates. Finally, our cohort population was selected at random from an urban population, in contrast to most other cohort studies in Japan, which have relied on rural populations.[7,8,19]

There may be some reasons why CKD is more positively associated with CVD in blacks or Japanese than in whites. Blacks and Japanese are more likely to have hypertension at an earlier age.[9,21] Therefore, the period of hypertension exposure tends to be longer in blacks and Japanese than in whites. The GFR estimation has been adjusted by a factor suitable for Japanese populations.[15]

Reduced kidney function is associated with increased levels of inflammatory factors,[22,23] abnormal apolipoprotein levels,[22] elevated plasma homocysteine,[22] enhanced coagulability,[23] anemia, left ventricular hypertrophy, increased arterial calcification, endothelial dysfunction, and arterial stiffness.[2,24] How these and other factors interact to increase the risk of adverse outcomes remains unclear but is the focus of ongoing investigations.[24]

Subjects with GFR levels of 50 to 59 mL/min/1.73m$^2$ were observed to be at risk for stroke. It is desirable to prevent CVD in subjects with both high-risk (<50 mL/min/1.73m$^2$) and less severe kidney disease (50 to 59 mL/min/1.73m$^2$), although an accelerated decline in GFR occurred for the subjects whose initial GFR <50 mL/min/1.73m$^2$.[25]

Hypertension is a strong risk factor for early decline in kidney function; hypertensive patients (BP ≥160/95 mm Hg) have a 5-fold greater decline in GFR (2.7 mL/min/1.73m$^2$/yr) compared with patients with BP <140/90 mm Hg.[26] Furthermore, in this study, the association between BP and the incidence of CVD were evident by CKD. The risk of CVD was higher in CKD subjects with normal and high-normal BP than in non-CKD subjects in the same BP categories. Using the combination of BP and CKD, it could be possible to screen more efficiently for higher risk of stroke and MI. This is compatible with the CKD clinical guidelines, which state that the preferable BP for subjects with CKD is 130/80 mm Hg.[27] For the prevention of CVD incidence for all hypertensive subjects in health check-ups, it might be desirable to measure serum creatinine levels and to intervene in lifestyle modification such as reducing salt intake, more frequent exercise, or quit smoking.

Our study has several limitations. The primary limitation is dilution bias,[28] in that the current study was based on single-day measurement of creatinine levels. The creatinine levels might have been misclassified, despite the fact that measurements of creatinine levels on a single day have been found to be accurate in other epidemiological studies. Second, we did not perform a creatinine clearance test or 2 measurements of serum creatinine at least 3 months apart. Although our definition of CKD is based on a single assessment of serum creatinine, the equation provides an accurate estimated GFR value.[15] Third, even with the moderate sample size (n=5494) and 12-year duration, the numbers of end points were limited, especially when the data were stratified by 2 variables, such as sex and glomerular filtration rates. A study with more participants with the same protocol is required to validate to the association between BP category and CVD by CKD.

In conclusion, CKD was associated with an increased risk for stroke and MI in a general urban Japanese population. Furthermore, the association between BP and CVD may be evident by CKD. To prevent the incidence of stroke and MI, it is necessary for subjects with CKD to control their BP by lifestyle modification and proper clinical treatment.

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## Disclosures

None.

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