Original Article

Prediction of Myocardial Infarction Using Coronary Risk Scores Among Japanese Male Workers: 3M Study

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Background: It remains unclear how much coronary risk factors contribute to the prediction of myocardial infarction among Japanese populations.

Methods and results: A nested case-control study of Japanese male workers aged 35 to 65 years was conducted between 1997 and 2000 in the Morbidity of Myocardial Infarction Multicenter Study in Japan (3M Study). Two hundred four myocardial infarctions were identified and two controls per case were selected by matching for age. We calculated odds ratios using a conditional logistic regression model, and constructed risk predictive models for the risk of myocardial infarction using coronary risk factors. The multivariable odds ratios (95 percent confidence intervals) of myocardial infarction were 2.02 (1.29–3.16) for high blood pressure, 2.33 (1.51–3.59) for high LDL-cholesterol, 4.16 (2.36–7.33) for low HDL-cholesterol, 1.49 (0.94–2.35) for high triglycerides, 1.46 (0.89–2.39) for high glucose, and 2.95 (1.90–4.59) for current smoking. A large reduction of the predictive value for myocardial infarction was shown after exclusion of high LDL-cholesterol (reduction of predictive value was –3.4%), further exclusion of low HDL-cholesterol (–7.1%), and further exclusion of current smoking (–16.4%).

Conclusions: High LDL-cholesterol and low HDL-cholesterol as well as current smoking had high predictive values for myocardial infarction among Japanese middle-aged male workers.

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Key words; Cholesterol, Myocardial infarction, Risk stratification

Introduction

Coronary heart disease is predicted to be one of

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the global leading causes of mortality and disability in the near future¹. The major pathological mechanism for coronary heart disease was atherosclerosis, the major risk factors of which have been established². The effect of a cluster of coronary risk factors has been stressed recently by study investigators³⁻⁵ and scientific committees⁶⁻¹⁰.

The impact of lipid profiles on coronary risk prediction has been well examined in Americans and

Europeans, whereas the data have been limited in Japanese populations, who have a lower incidence, mortality, and case-fatality rate of coronary heart disease¹¹⁻¹⁶. Previous studies showed that Japanese had a lower prevalence of obesity^{17, 18} and a lower contribution of serum total cholesterol to mortality from coronary heart disease, than Americans and Europeans¹⁹. However, the situation may be changing among Japanese middle-aged men: the mean values of total cholesterol levels and the incidence rate of coronary heart disease in an urban area have increased in the past half-century¹². It is uncertain how much coronary risk factors, in particular serum lipids, contribute to the prediction of myocardial infarction among Japanese populations.

Previous Japanese studies developed predictive models to prevent coronary heart disease^{4, 5, 10}. Although these predictive models included high blood pressure (hypertension) and high glucose (diabetes), predictive models including LDL- and HDL-cholesterol as well as smoking status have been limited.

We examined the prediction of coronary risk factors and evaluation of the predictive value for myocardial infarction among Japanese middle-aged male workers.

Materials and Methods

Study Population

The Morbidity of Myocardial Infarction Multi-center Study in Japan (3M Study) enrolled the 76 companies collaborating with a medical center of occupational physicians registered in seven districts of Japan in 1997. Details of the study methods were described elsewhere²⁰. In brief, the subjects were 133,099 workers (109,550 men, 23,549 women) from 41 workplaces (April 1994 to March 1997) and 257,440 workers (207,310 men, 50,130 women) from 76 workplaces (April 1997 to March 2000), aged 35 to 65 years. Coronary risk factor data were available from the annual health examinations conducted by companies as the baseline survey. We documented the incidence of myocardial infarction according to the criteria of World Health Organization Multinational MONItoring of trends and determinants in CARDiovascular disease Project (WHO MONICA Project)²¹ from April 1997 to March 2000.

Informed consent was obtained from the representatives of companies to conduct an epidemiological study, based on the guidelines of the Council for International Organizations of Medical Science²². The Committee of San-Yu-kai (Japan Association of Occupational Physicians) approved this study.

Case Determination of Myocardial Infarction

We used the criteria for myocardial infarction of the MONICA project²¹. The details of event registration are shown elsewhere²⁰. Briefly, occupational physicians affiliated to the surveyed companies received reports of absence or returns to work from business owners, and/or, if fatal, death certificates, when the participants had possibly suffered from myocardial infarction. The occupational physicians then asked for the hospital records of the candidate from the attending physician. We obtained the diagnostic data, including electrocardiograms before (<1 year) and after onset, and cardiac enzyme concentrations, date of onset, first medical consultation after the event, admission and discharge dates, survival at 28 days, previous history of coronary heart disease, and clinical diagnosis. We also obtained the death certificate and/or autopsy data for fatal cases. Silent myocardial infarctions were included as cases. Because almost all participants undertook annual health examinations with electrocardiograms, silent myocardial infarction within one year could be detected by changes in resting electrocardiogram (i.e. Q wave appearance). For the majority of patients, coronary arteriography and left ventriculography were performed during hospitalization, which we took into account for the diagnoses. Although recurrent cases (new events occurring more than 28 days after the previous myocardial infarction) were also registered, we excluded these cases from the present analysis because we aimed to develop the risk score of first events. Sudden death was defined as unexpected death within 24 hours of onset, a witnessed cardiac arrest, abrupt collapse not more than 24 hours earlier, or symptoms that precipitated the terminal event. We did not include individuals who had retired. Cases were registered with a registration form for myocardial infarction and sudden death in each collaborating medical center. All registered cases were reviewed independently by three cardiologists, and the final diagnosis was reached by consensus.

Age-Matched Nested Case-Control Study

A total of 296 fatal and nonfatal myocardial infarction cases were registered from April 1997 to March 2000. We excluded 92 case subjects (female, re-occurrent cases of myocardial infarction, and with missing coronary risk factor data), leaving 204 case subjects for analysis. The 28 day case-fatality rate of selected cases was 18.1%, which was similar to that reported from previous Japanese community-based studies¹⁴⁻¹⁶.

For each case of myocardial infarction, we randomly selected two controls, matched for age (± 2

years), from participants with no history of myocardial infarction until March 2000. Therefore, 612 male workers (204 case and 408 control subjects) were enrolled in the present study.

Coronary Risk Factors at Baseline Survey

We used health examination data within one year before the incidence of myocardial infarction for cases and from the same year for controls. The data included body height and weight, systolic and diastolic blood pressure, serum total cholesterol, HDL-cholesterol, triglycerides and glucose at fasting, medication use for hypertension, hyperlipidemia and diabetes mellitus, smoking status (never smoker, ex-smoker, and current smokers, including ≤ 20 cigarettes/day, 21–40 cigarettes/day and ≥ 41 cigarettes/day) and alcohol intake (never drinker, ex-drinker, and current drinkers, including < 23 g/day ethanol intake, 23–69 g/day and ≥ 69 g/day). Blood samples at fasting were collected from all participants. We calculated body mass index (BMI) as weight (kg) divided by the square of height in meters (m^2) and LDL-cholesterol by the Friedewald formula²³⁾ as $\text{LDL-cholesterol (mg/dL)} = \text{total cholesterol (mg/dL)} - \text{HDL-cholesterol (mg/dL)} - 0.2 * \text{triglycerides (mg/dL)}$.

The components of coronary risk factors were defined according to the guidelines of the Japan Atherosclerosis Society²⁴⁾ as follows: 1) high blood pressure: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or medication use, 2) high LDL-cholesterol: serum LDL-cholesterol ≥ 140 mg/dL (≥ 3.62 mmol/L) and/or medication use, 3) low HDL-cholesterol: serum HDL-cholesterol < 40 mg/dL (< 1.03 mmol/L), 4) high triglycerides: fasting serum triglycerides ≥ 150 mg/dL (≥ 1.69 mmol/L), 5) high glucose: fasting glucose ≥ 110 mg/dL (≥ 6.11 mmol/L) and/or medication use, and 6) current smoking.

Statistical Analysis

We used Student's *t* test and chi square test to compare the characteristics of case and control subjects. We calculated the age-matched and multivariable conditional odds ratio (OR) and 95% confidence interval (95%CI) of each of 6 coronary risk factors for myocardial infarction using a conditional logistic regression model. These coronary risk factors included high blood pressure, high LDL-cholesterol, low HDL-cholesterol, high triglycerides, high glucose, and current smoking. Because a previous study indicated some bias in LDL-cholesterol levels for fasting individuals with ≥ 802 mg/dL (≥ 8.8 mmol/L) triglycerides²⁵⁾, we conducted additional analysis after the

exclusion of one man with triglycerides ≥ 802 mg/dL and his controls.

We also conducted additional analysis using high total cholesterol instead of high LDL-cholesterol. We defined high total cholesterol as total cholesterol ≥ 224 mg/dL, because 140 mg/dL LDL-cholesterol corresponded to 224 mg/dL total cholesterol in the results of regression analysis.

We established three risk predictive models with these coronary risk factors: scoring in the unweighted additive model was calculated as adding 1 point; scoring in the weighted additive model was calculated as adding 1.5 to 4 points; and scoring in the weighted multiplicative model was calculated as multiplying 2 to 4 points. The weighted scores (1.5 to 4 points) were applied to the results of multivariable odds ratios.

We assessed the risk predictive models by receiver operating characteristic (ROC) curves and their respective areas under the curve (AUCs)²⁶⁾. The Hosmer-Lemeshow goodness-of-fit test was also used to assess the model fit.

All statistical tests were two-sided and *p*-value < 0.05 was regarded as significant. All statistical analyses were conducted using SAS, version 9.13 (SAS Institute, Inc., Cary, NC, USA).

Results

Compared with controls, myocardial infarction cases had the higher mean values of body mass index, systolic and diastolic blood pressures, fasting glucose, total and LDL-cholesterol and triglycerides and a lower mean value of HDL-cholesterol (**Table 1**). Cases were more likely to smoke and to use medication for diabetes. The prevalence of BMI ≥ 30.0 kg/ m^2 was only 3.9% in cases and 2.0% in controls.

A significantly increased risk of myocardial infarction was observed in each coronary risk factor in age-matched models (**Table 2**). After adjustment for other components, the multivariable odds ratios of myocardial infarction were 2.02 (1.29–3.16), $p = 0.002$ for high blood pressure, 2.33 (1.51–3.59), $p = 0.0001$ for high LDL-cholesterol, 4.16 (2.36–7.33), $p < 0.0001$ for low HDL-cholesterol, 1.49 (0.94–2.35), $p = 0.09$ for high triglycerides, 1.46 (0.89–2.39), $p = 0.13$ for high glucose, and 2.95 (1.90–4.59), $p < 0.0001$ for current smoking. The respective values for sensitivity and specificity were 47% and 70% for high blood pressure, 51% and 72% for high LDL-cholesterol, 33% and 94% for low HDL-cholesterol, 43% and 78% for high triglycerides, 29% and 84% for high glucose, and, 70% and 59% for current smoking.

These associations did not alter substantially after

Table 1. Characteristics of subjects in case and control groups

	Cases (<i>n</i> = 204)	Controls (<i>n</i> = 408)	<i>p</i> -value
	Mean ± SD/Percentage	Mean ± SD/Percentage	
Age, year	50.4 ± 5.3	50.4 ± 5.5	0.98
Height, cm	166.1 ± 5.4	169.2 ± 5.6	<0.0001
Weight, kg	65.9 ± 9.2	66.3 ± 8.8	0.56
Body Mass Index, kg/m ²	23.8 ± 2.9	23.2 ± 2.8	0.01
BMI ≥ 25.0 kg/m ² , %	28.4	20.1	0.02
BMI ≥ 30.0 kg/m ² , %	3.9	2.0	0.18
Systolic blood pressure, mmHg	134.1 ± 16.6	122.2 ± 17.7	<0.0001
Diastolic blood pressure, mmHg	82.3 ± 11.7	76.9 ± 11.6	<0.0001
Fasting blood glucose, mg/dL	110.3 ± 35.8	97.7 ± 16.8	<0.0001
Total cholesterol, mg/dL	221.4 ± 38.0	203.5 ± 32.7	<0.0001
LDL-cholesterol, mg/dL	139.0 ± 36.8	122.3 ± 30.8	<0.0001
HDL-cholesterol, mg/dL	46.1 ± 12.3	58.1 ± 13.8	<0.0001
Triglycerides, mg/dL	181.1 ± 132.5	115.9 ± 72.1	<0.0001
Current smoker, %	69.6	41.4	<0.0001
Current drinker, %	69.0	72.5	0.39
Medication use for hypertension, %	18.6	16.9	0.60
Medication use for diabetes, %	8.3	3.9	0.04
Medication use for hyperlipidemia, %	6.4	6.9	0.82

Table 2. Age-matched and multivariable odds ratios (OR) and 95% confidence intervals (95%CI) according to coronary risk factors

	No. of Controls	No. of cases	Age-matched OR (95%CI)	Multivariable OR (95%CI)
High blood pressure	123	95	2.08 (1.45–2.98)	2.02 (1.29–3.16)
High LDL-cholesterol	116	104	2.73 (1.89–3.95)	2.33 (1.51–3.59)
Low HDL-cholesterol	26	68	6.64 (3.98–11.08)	4.16 (2.36–7.33)
High triglycerides	91	88	2.63 (1.82–3.81)	1.49 (0.94–2.35)
High glucose	65	60	2.14 (1.43–3.18)	1.46 (0.89–2.39)
Current smoking	169	142	3.30 (2.26–4.81)	2.95 (1.90–4.59)

High blood pressure: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or hypertensive medication use.

High LDL-cholesterol: LDL-cholesterol ≥ 140 mg/dL and/or hyperlipidemic medication use.

Low HDL-cholesterol: HDL-cholesterol < 40 mg/dL

High triglycerides: triglycerides ≥ 150 mg/dL

High glucose: fasting glucose ≥ 110 mmHg and/or diabetic medication use.

the exclusion of one man with hypertriglyceridemia and his controls: the multivariable odds ratios of myocardial infarction were 2.01 (1.28–3.15), $p=0.002$ for high blood pressure, 2.32 (1.50–3.56), $p=0.0001$ for high LDL-cholesterol, 4.17 (2.36–7.34), $p<0.0001$ for low HDL-cholesterol, 1.48 (0.93–2.33), $p=0.10$ for high triglycerides, 1.45 (0.88–2.37), $p=0.14$ for high glucose, and 2.94 (1.89–4.58), $p<0.0001$ for current smoking.

We constructed three risk predictive models with

the coronary risk factors (**Table 3**). The weighted risk scores (1.5 to 4 points) were applied to the results of multivariable odds ratios: 1.5 points for high triglycerides and high glucose, 2 points for high blood pressure, 2.5 points for high LDL-cholesterol, 3 points for current smoking, and 4 points for low HDL-cholesterol.

When the risk scores increased, increased risks were observed linearly for myocardial infarction in three risk predictive models (**Table 4**). Adjustment for

Table 3. Calculation using three risk score models

	Unweighted additive model	Weighted additive model	Weighted multiplicative model
High blood pressure	+ 1 points	+ 2 points	X2 points
High LDL-cholesterol	+ 1 points	+ 2.5 points	X2.5 points
Low HDL-cholesterol	+ 1 points	+ 4 points	X4 points
High triglycerides	+ 1 points	+ 1.5 points	X1.5 points
High glucose	+ 1 points	+ 1.5 points	X1.5 points
Current smoking	+ 1 points	+ 3 points	X3 points

Table 4. Age-matched and multivariable odds ratio (OR) and 95% confidence interval (95%CI) according to three risk predictive models

	Quartiles of risk scores			
	1 (Lowest)	2	3	4 (Highest)
Unweighted additive model				
Range, point	0	1	2	3-6
No. of control subjects	97	132	104	75
No. of case subjects	11	29	47	117
Age-matched OR (95%CI)	1.0	2.19 (1.02-4.72)	3.85 (1.80-8.23)	15.3 (7.17-32.5)
Multivariable OR (95%CI)*	1.0	2.84 (1.23-6.57)	4.32 (1.90-9.84)	19.2 (8.07-45.5)
Weighted additive model				
Range, point	0	1.5-3.0	3.5-5.0	5.5-14.5
No. of control subjects	97	134	78	99
No. of case subjects	11	29	25	139
Age-matched OR (95%CI)	1.0	2.13 (0.99-4.58)	3.06 (1.36-6.87)	12.6 (6.08-26.2)
Multivariable OR (95%CI)*	1.0	2.61 (1.12-6.07)	3.19 (1.32-7.73)	15.2 (6.64-35.0)
Weighted multiplicative model				
Range, point	1.0	1.5-3.0	3.75-6.75	7.5-135.0
No. of control subjects	97	149	69	93
No. of case subjects	11	32	30	131
Age-matched OR (95%CI)	1.0	2.12 (0.99-4.52)	4.32 (1.91-9.75)	12.4 (5.96-25.8)
Multivariable OR (95%CI)*	1.0	2.53 (1.11-5.74)	4.67 (1.91-11.42)	13.7 (6.05-30.9)

*Adjusted for body mass index (kg/m²) and alcohol intake category (non-drinker, habitual drinker, < 23 g/day ethanol intake, 23-69 g/day and ≥ 69 g/day).

other coronary risk factors did not alter these associations materially. The multivariable odds ratio (95%CI) for the highest versus lowest risk scores was 19.2 (8.07-45.5), $p < 0.0001$ in the unweighted additive model, 15.2 (6.64-35.0), $p < 0.0001$ in the weighted additive model, and 13.7 (6.05-30.9), $p < 0.0001$ in the weighted multiplicative model. These associations were essentially the same after the exclusion of one man with hypertriglyceridemia and his controls.

According to the ROC curve, the weighted additive model ($p = 0.94$) and unweighted additive model ($p = 0.94$) had better fitness than the weighted multiplicative model ($p < 0.0001$), whereas both the

weighted additive model (AUCs=0.773) and weighted multiplicative model (AUCs=0.772) had the higher predictive value than the unweighted additive model (AUCs=0.755) (not shown in the tables).

When high LDL-cholesterol, low HDL-cholesterol and current smoking were excluded from the weighted additive models, the predictive value fell substantially (**Fig. 1**). Compared with the weighted additive model of all 6 components (AUC=0.773), the c-statistic was reduced in the weighted additive model excluding high LDL-cholesterol (AUC=0.747: the reduction of the predictive value was -3.4%), further excluding low HDL-cholesterol (AUC=0.718:

Fig. 1. Receiver operating characteristic (ROC) curves and their respective areas under the curve (AUCs) of weighted additive models when high LDL-cholesterol, low HDL-cholesterol, and current smoking were excluded. The p -value of the Hosmer-Lemeshow goodness-of-fit test for each model was >0.20 , which showed no evidence of a lack of fit in the selected models.

-7.1%), and further excluding current smoking ($AUC=0.646$; -16.4%).

The predictive value was not substantially altered in additional analysis using high total cholesterol instead of high LDL-cholesterol. The AUC in the weighted additive model was 0.771 ($p=0.94$) using high total cholesterol and 0.773 ($p=0.94$) using high LDL-cholesterol.

Discussion

In this large case-control study of Japanese male workers, we showed the importance of high LDL-cholesterol and low HDL-cholesterol as well as current smoking in the risk prediction of myocardial infarction. When these three components were excluded, the predictive value for coronary risks was markedly reduced. Although the criteria of metabolic syndrome do not include LDL-cholesterol and current smoking as a predictive risk factor⁸⁻¹⁰, our data showed that these three risk factors are important to predict myocardial infarction among Japanese men.

The predictive value did not substantially alter when we used high total cholesterol instead of high

LDL-cholesterol. A recent investigation of the Framingham risk score also showed that the use of LDL-cholesterol, instead of total cholesterol, did not improve model fit or performance²⁷. Thus, these results suggest that we could use either high total cholesterol or high LDL-cholesterol as a component to calculate coronary risk scores.

The positive association between total cholesterol and mortality from coronary heart disease was not observed in a Japanese rural cohort, initiated from 1958¹⁹, but another Japanese cohort study of urban male workers (mean total cholesterol 194 mg/dL) initiated from 1979 showed significant associations of high total and low HDL-cholesterol with an increased risk of coronary heart disease²⁸. Serum cholesterol levels in Japanese have increased since the 1960s¹¹) and are approaching the levels in the United States^{29, 30}. The increase in population levels of total cholesterol in Japanese may make cholesterol an important risk factor for coronary heart disease¹². Our study extended the evidence that high LDL-cholesterol and low HDL-cholesterol greatly contribute to the prediction of myocardial infarction among Japanese middle-aged male workers.

We found some variation in ROC curves among three risk predictive models. Model fitness in both unweighted and weighted additive models was higher than in weighted multiplicative models, while c -statistics in these ROC curves were higher in weighted additive and multiplicative models than in unweighted additive models. The Framingham risk score and others³⁻⁵) used a risk predictive model by adding the weighted score of each risk factor, whereas other scores, such as that for metabolic syndrome⁶⁻¹⁰), used unweighted scores. The Framingham risk score was a better predictor of the risk of coronary heart disease than the metabolic syndrome score³¹). These results suggested that the risk predictive model with weighted scores may be more suitable for risk prediction, compared with unweighted scores, implying that we need to pay attention to the magnitude of each risk factor, as well as the number of risk factors in clinical practice.

Previous studies (e.g. NIPPON DATA 80 and the Ibaraki Prefectural Health Study) developed risk scores for the prediction of mortality from coronary heart disease in the Japanese general population^{4, 5}), but mortality was only part of the incidence of myocardial infarction¹⁴⁻¹⁶). The present study has developed the first risk scores for predicting myocardial infarction in Japanese men.

The strengths of the present study included the large sample of middle-aged Japanese men, who had a

low prevalence of obesity and a low incidence, mortality, and case-fatality rate of myocardial infarction¹¹⁻¹⁶. The mean value of total cholesterol was 200 mg/dL and the prevalence of obesity (BMI ≥ 30 kg/m²) was 2.0% among controls. The population levels of these coronary risk factors were consistent with the results of a Japanese national survey³²⁾ and were lower than in other developed countries¹⁷⁻¹⁹⁾.

A limitation of the current study is that we used health screening data from 76 companies in which serum lipids were measured by multiple laboratories; however, these laboratories had been quality controlled for lipid measurement by the National Federation of Industrial Health Organizations.

In conclusion, the present study provides epidemiological evidence that high LDL-cholesterol and low HDL-cholesterol as well as current smoking had a high predictive value for myocardial infarction among middle-aged Japanese male workers.

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Appendix 1

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