

# Multiple Risk Factor Syndrome In Japanese Male Workers: A Work-Site Cohort Study

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## Citation

H Sugimori, K Yoshida, Y Yamada, C Hamashima, T Izuno, M Suka, T Tanaka, H Kawaguchi, Y Iida. *Multiple Risk Factor Syndrome In Japanese Male Workers: A Work-Site Cohort Study*. The Internet Journal of Internal Medicine. 2002 Volume 3 Number 2.

## Abstract

**Objectives:** To demonstrate the relationships between multiple risk factor syndrome (MRFS) and atherosclerotic events, comparing with hypercholesterolemia group (hTC), in Japanese male workers by conducting a work-site cohort study.

**Methods:** From 1986 to 1992, 163 male eligible subjects (MRFS group: n=87; hTC group: n=76) aged 30 years or more, working at a single department store in Tokyo were enrolled, and followed-up until 1998 to observe the occurrence of atherosclerotic events (coronary heart diseases, cerebral infarctions and retinal artery hemorrhages). We defined MRFS group as subjects who met the following criteria: high blood pressure (diastolic blood pressure  $\geq 90$  mmHg and/or systolic blood pressure  $\geq 150$  mmHg, or the initiation of hypertension therapy), hypertriglyceridemia (serum triglycerides  $\geq 160$  mg/dl), hyperglycemia (defined by the criteria by Japan Diabetes Society, 1970), and obesity (BMI:  $\geq 24.0$  kg/m<sup>2</sup>) at baseline. To compare MRFS group, we also defined hTC group as subjects whose serum total cholesterol level at baseline was 280 mg/dl or more.

**Results:** Eight coronary heart disease cases, 3 cerebral infarction cases and 4 retinal artery hemorrhage cases were observed in MRFS group. On the other hand, no atherosclerotic case was observed in hTC group during the period. Mantel-Haenszel procedure showed that age-adjusted atherosclerosis incidence was significantly higher in MRFS group than that in hTC group ( $p < 0.05$ ).

**Conclusions:** MRFS group are more likely to experience atherosclerotic events compared with hTC group. It is important to focus on health education regarding atherosclerotic outcome prevention towards a cluster of metabolic risk factors, MRFS, in work-site as well as severe hypercholesterolemia.

## ABBREVIATION

BMI: Body mass index

## INTRODUCTION

In recent years it has been proposed that hypertension is part of a cluster of metabolic risk factors involving hyperlipidemia and hyperglycemia, with hyperinsulinemia as the common link<sup>1,2</sup>. The link is known as 'Multiple Risk Factor Syndrome (MRFS)' or 'Metabolic Syndrome X'<sup>1</sup> or 'Deadly Quartet'<sup>3</sup>, or 'Insulin Resistant Syndrome'<sup>2</sup>. Furthermore, researchers also reported close relationships

between MRFS and systemic atherosclerotic vascular disease such as coronary heart disease (CHD)<sup>3</sup>.

However, in Japan few longitudinal studies have undergone assessment of the risk of MRFS regarding atherosclerotic vascular outcomes. The majority of the studies have concentrated on selected clinical sample, and it appears that either limited or no data have been demonstrated by epidemiological studies such as a work-site based study.

Moreover, although hypercholesterolemia has been already established as a risk factor of CHD and managed intensely

and routinely in work-site, a cluster of subclinical metabolic risk factors seemed to be passed by and noticed insufficiently. One main purpose of this study is to strike a note of warning to health care professionals against such a cluster, MRFS. Therefore, we designed this study to focus on the comparison between MRFS and severe hypercholesterolemia in this study in terms of occurrence of atherosclerotic events in Japanese middle-aged male workers,.

### SUBJECTS AND METHODS

We conducted a work-site cohort study at a single department store company in Tokyo. From 1986 to 1992, the company had an average annual participation of 2849 male employees in the regular health-checkups. Of those health screened, 206 male participants, aged 30 years or more at baseline, were designed to allocate into the two groups by the following criteria: MRFS group and hTC group. However, since 6 subjects met both criteria and 37 subjects in hTC group had been initiated medication during follow-up period, we excluded 43 cases from the analysis. Thus, 163 final eligible subjects (MRFS group: n=87; hTC group: n=76) were enrolled into this study, and followed up until 1998 over 6 years on average to observe the occurrence of three atherosclerotic events: CHD, cerebral infarctions and retinal artery hemorrhages.

To compare with hTC group, we defined MRFS group, by referring to the “Deadly Quartet”<sup>3</sup>, as subjects who met all of the following criteria in the initial year (baseline): high blood pressure recorded on at least two measurements (diastolic blood pressure  $\geq 90$  mmHg and/or systolic blood pressure  $\geq 150$  mmHg, or the initiation of anti-hypertension therapy), hypertriglyceridemia (serum triglycerides: TG  $\geq 160$  mg/dl), hyperglycemia (defined by the criteria by Japan Diabetes Society, 1970, see [Note]), and obesity (body mass index: BMI  $\geq 24.0$  kg/m<sup>2</sup>). On the other, we defined hTC group as subjects whose serum total cholesterol level (TC) was severe ( $\geq 280$  mg/dl or more) at the initial year<sup>4</sup>. All subjects were from similar socioeconomic and occupational background (i.e. sales person), and all were physically active at baseline (without clinical evidence of cardiovascular, cerebrovascular, and renal disease, history of receiving any medical treatment).

Blood pressure was measured on the right arm with the participant in a sitting position, and after 4 minutes rest using a calibrated mercury sphygmomanometer. BMI is expressed as weight (kilograms) per height (meters) squared.

Weight and height was measured without shoes and in light clothing. The blood samples of lipids were obtained after an overnight fasting of 10 to 14 hours on the morning (around 8 AM). All biochemical assays were completed by using an automated autoanalyzer (HITACHI Co., Ltd. type 7250) at Mitsukoshi Multiphasic Health Testing and Service (Mitsukoshi Health and Welfare Foundation, Tokyo) where quality control of blood sample analysis have been certificated by The Japan Society of Multiphasic Health Testing and Service (JMHTS). Blood samples were analyzed with popular standardized reagents in Japan:

DETERMINER-L TC2 (KYOWA MEDEX Co., Ltd.) for total cholesterol and high-density lipoprotein cholesterol, TG-L (SEROTEC Co., Ltd.) for triglycerides, and CICALIQUID GLUCOSE for glucose (KANTO KAGAKU Co).

[Note] Hyperglycemia is diagnosed as ‘diabetic’ or ‘impaired glycemia’ as follows: ‘diabetic’ type is defined when fasting plasma glucose (FPG) is 140 mg/dl or higher, and/or plasma glucose 2 hour after 75 glucose load (2hPG) is 200 mg/dl or higher. Casual plasma glucose higher than 200 mg/dl is also regarded as indicating diabetic type. Normal type is defined when FPG is below 110 mg/dl and 2hPG below 140 mg/dl; ‘impaired glycemia (borderline type)’ is defined in those who belong neither to diabetic nor to normal type.<sup>5</sup>

The presence of CHD was defined as an event of myocardial infarction and angina pectoris diagnosed by cardiologists with cardio-angiography (CAG). The presence of cerebral infarction was defined as an event of cerebral infarction diagnosed with magnetic resonance imaging (MRI). The presence of eyeground bleeding was diagnosed by ophthalmologists with the regular eyeground checkups as a part of the regular health-checkups. These events were confirmed by reviewing of both personnel management records and medical records, by an occupational physician in this company.

First, we compared the characteristics concerning the risk factors of atherosclerosis between MRFS group and hTC group. In both groups, frequencies of 9 risk factors for atherosclerosis, that is BMI, blood pressure, TC, TG, glucose tolerance, liver function, serum uric acid (UA), alcohol drinking habits, smoking habits were evaluated. Furthermore, the atherogenic index ( / HDL) were assessed where “HDL” identifies high-density lipoprotein cholesterol.

In this study, mean age of baseline in MRFS group (46.7 $\pm$ 7.1 year old) was significantly higher than that in hTC

group (42.7±7.3 year old). To adjust age confounding regarding occurrence of atherosclerotic events, we used Mantel-Haenszel procedure (we used 0.5 instead of 0 for the cell value in the approximate calculations).

Statistical analysis was performed by using SAS programs Version 6.12 (SAS Institute, Cary, NC.) . Our study was conducted in accordance with the recommendations outlined in the Declaration of Helsinki (revised in 1983, 2000) and an ILO code of practice in 1997 (the Protection of worker's personal data).

**RESULTS**

Table 1 demonstrates the characteristics of both MRFS group and hTC group at baseline. Differences between both groups in blood pressure, BMI, glucose tolerance, and TG were statically significant. (p<0.05) Differences in other risk factors, that is liver function, UA, alcohol habits, and smoking habits were not significant. The observational period also showed no statistical significance. Consequently, according to the definition, although the atherogenic score was lower in MRFS group, total number of risk factors was higher in MRFS group compared with hTC group.

**Figure 1**

item	criteria	MRFS group (n=87)		hTC group (n=76)		chi-square test
		n	%	n	%	
blood pressure therapy	SBP>139 mmHg and/or DBP>95 mmHg or BM-I	87	100.0%	15	19.7%	*
BMI	BM-I>24 kg/m <sup>2</sup>	87	100.0%	52	68.4%	*
glucose intolerance <sup>1</sup>		87	100.0%	20	26.3%	*
serum total cholesterol (TC)	TC>240 mg/dl	53	60.9%	76	100.0%	*
serum triglycerides (TG)	TG>160 mg/dl	87	100.0%	69	90.8%	*
serum uric acid (UA)	UA>8.0 mg/dl and/or ALT>40 IU/L and/or AST>40 IU/L	38	43.7%	22	28.9%	NS
liver function		65	74.7%	51	67.1%	NS
smoking habits	smoker	29	33.3%	32	42.1%	NS
alcohol habits	drinking habits: every day	46	52.9%	33	43.4%	NS
		mean	SD	mean	SD	t-test
atherogenic index		4.1	1.2	5.2	2.0	*

SD: definition of diabetic or impaired glucose tolerance by 75g OGTT were shown in the text.  
Abbreviations: MRFS: Multiple risk factors syndrome, hTC: high total cholesterol, SBP: systolic blood pressure (mmHg), DBP: diastolic blood pressure (mmHg), BMI: body mass index, ALT: aspartate aminotransferase, AST: alanine aminotransferase.  
\* p<0.05

Table 2 shows the numbers of atherosclerotic events during the follow-up period. In MRFS group 8 CHD cases (9.2%), 3 cerebral infarction cases (3.4%) and 4 retinal artery hemorrhage cases (4.6%), for a total of 15 (17.2%) atherosclerotic events were observed during the average 6.8 years of follow-up. Incidence of atherosclerotic events increased with age strata. On the contrary, none of atherosclerotic events was observed in hTC group during the average 7.9 years of follow-up. Mantel-Haenszel procedure showed that age-adjusted atherosclerosis incidence was significantly higher in MRFS group than that in hTC group (p<0.05).

**Figure 3**

Age	MRFS				hTC		Fisher's Exact Probability Test
	cardiovascular disease	infarction	artery hemorrhage	total			
30-39y	0	0	3	3 / 31 9.7%	0 / 13	0.0%	*
40-49y	3	2	1	6 / 43 14.0%	0 / 37	0.0%	*
50- y	5	1	0	6 / 13 46.2%	0 / 12	0.0%	NS
total	8	3	4	15 / 87 17.2%	0 / 76	0.0%	**

\* p-value was calculated by Mantel-Haenszel procedure (denote that 0.5 was used instead of 0 in the approximate calculations)

No atherosclerotic event occurred in the 6 MRFS/hTC participants who had been excluded from study subjects due to meeting both criteria. No death case was observed in both MRFS group and hTC group.

{image:3}

**DISCUSSION**

This work site cohort study demonstrated close relationships between MRFS and the occurrence of atherosclerotic events in Japanese male workers, comparing with the severe hypercholesterolemia group. In Japan, workers tend to work in the same company for a long time, that is 'life-long employment', and workers in this study are no exception. It is rational and worthy to utilize the health-checkups data in work site and to conduct a longitudinal epidemiological study for elucidating health risks in work-site.

Fifteen atherosclerosis events had occurred in MRFS group while no atherosclerotic case emerged in hTC group. Results from the large trial (MRFIT) suggested that diabetes is a strong, independent risk factor for CHD mortality over and above the effect of TC, blood pressure, and smoking habits . Therefore, although our outcome value was morbidity, one possible reason for incidence difference between both groups might be explained by the existence of hyperglycemia. Moreover, Haffner et al. demonstrated type-2 diabetic subjects even without clinical CHD had extensive atherosclerosis in the carotid artery, which is similar to non-diabetic patients with clinical CHD . Although our criteria contained not only established diabetes but subclinical cases, namely 'impaired glycemia (borderline type)', the recent study , showed that no apparent threshold effect in glycated hemoglobin A1c (HbA1c) existed in terms of mortality and concluded importance of preventive efforts in a subclinical group. Hyperglycemia is one of the main component of MRFS, which might be attributable to increase atherosclerotic incidence in MRFS group. Early preventive intervention for "" including education in the work site is strongly recommended.

The relationships of hypercholesterolemia to atherosclerotic events, such as CHD are now well established<sup>10</sup>. However, although CHD and stroke share many of the same risk factors, the relationship of cholesterol to stroke remains controversial<sup>11</sup>. This might be alternative reason for the risk difference between MRFS group and hTC group.

Our study presents several limitations: the short period of follow-up, the limited number of events, the truncation and the potential bias such as selection bias and measurement bias. It should be noted that the number of atherosclerotic events in MRFS group was only 15 cases, and, as consequence, the reliability and the stability of risk difference are not fully taken in. In addition, since we defined the both groups by a single measurement of each component data per person (baseline), thus tending to produce misclassification (regression dilution bias)<sup>12</sup>.

We excluded 37 participants who had initiated medication during follow-up and this might be another limitation for our study. Difference between this excluded 37 medicated participants and 76 eligible hTC subjects in the frequencies of high blood pressure showed statistically significant. (19.7% vs. 37.8%). However, differences in the mean TC level, BMI, glucose intolerance, TC, TG, smoking habits, alcohol habits were similar in both groups and did not reach statistically significance.

In summary, we found that atherosclerotic events occur more frequently in MRFS than in hTC group in worksite. In Japan, both cardio- and cerebro-vascular disease is major part of the public health concerns, because of its high prevalence and its unfavorable QOL due to a marked degree of consequent disability. Our findings suggest that a cluster of subclinical metabolic risk factors accelerate occurrences of atherosclerotic outcome, and we should focus intensely on a linkage of those risks, that is hyperglycemia, high blood pressure, obesity, and hypertriglyceridemia, as well as single hypercholesterolemia that is known widely as a potential atherosclerotic risk factor. Although this is a preliminary study and has several study limitations, our results may provide an important clue to prevent atherosclerosis events in occupational fields.

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