

Relationship between metabolic risk factor clustering and cardiovascular mortality stratified by high blood glucose and obesity: NIPPON DATA90, 1990-99

A Short Running Title: Metabolic factor clustering and CVD mortality

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Abstract

Objective

Metabolic syndrome (MS) is diagnosed according to several criteria. Among them, some require glucose intolerance and the others require obesity for diagnosing MS. We investigated the relationship between metabolic risk factor clustering and cardiovascular disease (CVD) mortality stratified by high blood glucose or obesity.

Research design and methods

We followed 7,219 Japanese men and women without a history of CVD for 9.6 years. We defined high blood pressure, high blood glucose, high triglycerides, low high-density lipoprotein cholesterol and obesity as metabolic factors. The multivariate adjusted hazard ratio (HR) for CVD mortality according to the number of clustering metabolic factors was calculated using the Cox proportional hazards model.

Results

During follow-up, 173 participants died of CVD. The numbers of metabolic risk factors and CVD mortality were positively correlated (P for trend = 0.07). The HR was obviously higher among participants with, than without high blood glucose and clustering of ≥ 2 other metabolic risk factors (HR = 3.67, CI, 1.49-9.03). However, the risk increase was only modest in participants without high blood glucose even if they had ≥ 2 other metabolic risk factors (HR = 1.99, CI, 0.93-4.28). Conversely, metabolic risk factor clustering was related to CVD mortality irrespective of obesity.

Conclusions

Our findings suggest that glucose tolerance plays an important role in CVD mortality. Since the prevalence of non-obese participants with several metabolic risk factors was quite high and their CVD risk was high, excluding them from MS due to the absence of obesity might overlook their risk.

Introduction

The World Health Organization states that individual risk factors for cardiovascular disease (CVD) convey greater CVD risk. Furthermore, even though each one of these risk factors alone is not serious, the risk becomes more “powerful” when they are combined (1). Metabolic syndrome is the concept of clustering risk factors comprising insulin resistance, abdominal fat distribution, dyslipidemia and hypertension. (2-5).

Several institutions have established their own diagnostic criteria for metabolic syndrome. The National Cholesterol Education Program (NCEP) considers that each metabolic factor has the same importance (6), whereas the World Health Organization (WHO) requires impaired glucose tolerance among its criteria to diagnose metabolic syndrome (7). Finally, the International Diabetes Federation (IDF) and the Japanese guidelines require central obesity defined by waist circumference to diagnose metabolic syndrome (8, 9). Thus, whether a relationship between metabolic risk factor clustering and CVD mortality differs according to obesity or impaired glucose tolerance, which are both required for a diagnosis of metabolic syndrome, should be determined.

The present study investigates the association between metabolic factor clustering and CVD mortality stratified

according to obesity or impaired glucose tolerance in a population-based cohort study in the Japanese general population.

Method

Population

Cohort studies of the National Survey on Circulatory Disorders, Japan, are referred to as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged). NIPPON DATA includes two cohort studies. Baseline data were surveyed in 1980 and in 1990 (NIPPON DATA80 and NIPPON DATA90) and the details of these cohorts have been reported (10-15). Here, we analyzed data from NIPPON DATA90 because the baseline survey of NIPPON DATA80 does not include some important metabolic factors such as high-density lipoprotein cholesterol (HDL-C).

A total of 8,384 residents (3,504 men and 4,880 women, aged \geq 30) from 300 randomly selected districts participated in the survey and were followed until November 15th, 2000. The participation rate in this survey was 76.5%. Of the 8,384 participants, 1,165 were excluded because of a history of coronary heart disease or stroke (n = 371), information missing at the baseline survey (n = 636) and failure to access due to incomplete residential access information at the first survey (n = 158). The remaining 7,219 participants (2,999 men and 4,220

women) were included in the analysis.

Follow-up survey

The underlying causes of death in the National Vital Statistics were coded according to the 9th International Classification of Diseases (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the start of 1995 until the end of 1999. Details of these classifications are described elsewhere (10-15).

The Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000) approved this study.

Baseline examination

Non-fasting blood samples were obtained at the baseline survey. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to one laboratory (SRL, Tokyo) for blood measurements. Plasma glucose was measured enzymatically. Serum triglycerides (TG) and total cholesterol were also measured enzymatically and high-density lipoprotein cholesterol (HDL-C) was measured after heparin-calcium precipitation (16).

Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Baseline blood pressure was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants. Public

health nurses obtained information on smoking, alcohol consumption, physical activity and medical history. We divided participants into four categories of smokers (never-smoked; ex-smoker; current smoker, <20 and ≥ 20 cigarettes/day) and six categories of drinking (never-drinker; ex-drinker; current drinker 1, 2, 3, and 4 gou of sake/day); 1 gou (180 ml) is equivalent to 23 g of alcohol (11). We divided participants into three categories of physical activity (yes, no for physical problems, no for any other reasons).

We defined metabolic factors as follows: obesity, BMI ≥ 25 kg/m²; high blood pressure, systolic blood pressure of ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, administration of antihypertensive agents, or any combination of these; high blood glucose, serum glucose ≥ 140 mg/dl, medication for diabetes or both. Because our samples were non-fasting, the blood glucose level of post load for diagnosis of impaired glucose tolerance was ≥ 140 mg/dl (17). We defined high triglycerides as non-fasting serum triglyceride ≥ 200 mg/dl and also as being medicated for dyslipidemia. Low HDL-C was defined as serum HDL-C ≤ 40 mg/dl for men, and ≤ 50 mg/dl for women.

Statistical analysis

Continuous variables were compared using the analysis of variance and the χ^2 -test compared the dichotomized

variables to examine differences in baseline characteristics of participants according to the numbers of clustering metabolic factors.

The multivariate adjusted hazard ratio (HR) of all CVD mortality for each group was calculated using the Cox proportional hazards model adjusted for age, sex, total cholesterol, smoking, drinking and physical activity category. When we calculated HR for individual component of metabolic factor, we further adjusted for other components of metabolic factor. We used non-obese participants without any metabolic factor or participants with neither metabolic factor nor high blood glucose as references in analyses stratified by obesity or high blood glucose (required component by IDF and WHO respectively). Since leaner participants also have a higher CVD mortality risk in Japan, we further analyzed a data subset excluding leaner participants (BMI <18.5 kg/m²) (18,19).

All confidence intervals (CIs) were estimated at the 95% level. A P-value of <0.05 was considered significant. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 11.0J, Tokyo, Japan) performed all analyses.

Results

Table 1 shows the baseline characteristics of the study participants according to the numbers of metabolic factors.

Total person-years were 69,170 and the

mean follow-up period was 9.6 years.

During follow-up, 625 participants died of all causes and 173 of CVD. Table 2 shows the multiple adjusted HRs and 95% CIs according to individual components of metabolic risk factors.

Table 3 shows the number of deaths, multiple adjusted HRs and 95% CIs according to various numbers of metabolic factors. The HRs for CVD mortality were higher in the group with more metabolic factors but the trend was not statistically significant (P for trend = 0.074). The relationship between numbers of risk factors and CVD mortality did not differ according to gender (P for interaction=0.70). We therefore combined men and women in the following analyses. The tendency for HR to be higher in those with more metabolic factors was similar for heart disease (3 risk factors: HR = 2.08, CI, 0.67-6.48; 4 risk factors: HR = 3.97, CI, 1.24-12.72; 5 risk: HR = N.A., CI, N.A.) and stroke (3 risk factors: HR = 2.07, CI, 0.67-6.37; 4 risk factors: HR = 1.23, CI, 0.30-5.05; 5 risk factors: HR = 6.26, CI, 1.13-34.60) mortality. The HR tendency for all cause mortality was similar but the number of clustering metabolic factors was not significantly related to all-cause mortality (3 risk: HR = 1.16, CI: 0.81-1.65; 4 risk: HR = 1.18, CI: 0.77-1.80; 5 risk: HR = 1.44, CI: 0.57-3.63).

Table 4(A) shows multiple adjusted HRs and 95% CIs due to the number of

metabolic factors except high blood glucose stratified by high blood glucose. The HRs trended to increase in both groups (with and without high blood glucose). The HR of CVD in participants with three and more metabolic factors but high blood glucose was modest and not statistically significant. Conversely, HRs were obviously higher in participants with high blood glucose and 2 and more other metabolic factors than those with participants with neither metabolic factors nor high blood glucose. The risk increases were statistically significant.

Table 4(B) shows multiple adjusted HRs and 95% CIs for CVD mortality according to the number of metabolic factors other than obesity stratified by obesity. The relationship between HRs and the numbers of metabolic factors was positive in both obese and non-obese groups. This relationship was unchanged when participants with lower BMI (<18.5 kg/m²) were excluded.

Discussion

We found that metabolic factor clustering was positively associated with CVD mortality in the general Japanese population. The risk increase in participants with both high blood glucose and two or more metabolic factors was significantly higher than in those with neither high blood glucose nor metabolic risk factors. The risk in non-obese participants with more metabolic factors was also increased.

Although investigating the relationship between metabolic factor clustering and CVD mortality is important, prospective studies on the topic are still scarce. Based on the NCEP and WHO definition of metabolic syndrome, several investigators have reported that participants with metabolic syndrome or metabolic factor clustering have a high HR of CVD mortality (20-25). Ford summarized prospective cohort studies and reported that the HRs of CVD mortality were 1.65 (1.38-1.99) according to the NCEP definition and 1.93 (1.39-2.67) according to the WHO definition, respectively (26). This is consistent with our findings that participants with more metabolic factors have a higher risk of CVD mortality. Our results were also comparable with those of a prospective study in Japan that found the relative risk of cardiac diseases was 2.23 (1.14-4.34) in participants with three or more metabolic factors compared with that in participants with less than three metabolic factors (27).

The IDF definition requires obesity for diagnosis of metabolic syndrome. These guidelines explain that central (abdominal) obesity is prerequisite for this diagnosis because it is easy to assess and independently associated with each of the other metabolic syndrome components (8). The IDF guidelines do not essentially require insulin resistance since it is difficult to measure in day-to-day clinical practice (7,8). However, although

increased waist circumference is an important component of metabolic syndrome, some individuals with multiple risk factors and an increased risk of CVD mortality have normal waist circumference (28,29). For example, Katzmarzyk, et al. reported that waist circumference is a valuable component of metabolic syndrome, but they also raised the concern that the IDF requirement of an increased waist circumference warranted caution because a large proportion of individuals with normal waist circumference also have multiple risk factors and an increased risk of mortality (28).

We found here that non-obese participants with three or more metabolic factors had significantly higher HRs for CVD death and that their risk was similar to that of obese participants with the corresponding number of metabolic factors. Thus, a proportion of high-risk participants might be overlooked if obesity is a diagnostic requirement for metabolic syndrome. Waist circumference supposedly indicates visceral fat more accurately than BMI in terms of predicting diabetes mellitus (30). However, we did not have any information about waist circumference and used BMI as it closely correlates with waist circumference. Furthermore, BMI has been used to diagnose obesity in many epidemiological studies of metabolic syndrome (22,23), indicating that BMI was acceptable for

our purposes. However, because the use of BMI, we might have underestimated the impact of obesity on CVD mortality. A similar study using waist circumference should clarify the relation.

The WHO guidelines indicate that the presence of diabetes, impaired glucose tolerance, or insulin resistance is necessary for a diagnosis of metabolic syndrome because this condition is considered a special classification for those with the potential for diabetes (manifested as impaired glucose tolerance, impaired fasting glucose, or insulin resistance determined using the hyperinsulinemic euglycemic clamp) (1,7). Here, we also stratified participants according to blood glucose level and found that the HR was higher among those with, than without high blood glucose. These findings suggest that glucose tolerance plays an important role in CVD mortality. Some reports have shown higher HRs when using the WHO, rather than the NCEP definition of metabolic syndrome. This means that the participants with impaired glucose tolerance have higher HRs, a finding which the present results support (26). However, several participants with clustering of metabolic factors other than impaired glucose tolerance also had an increased risk of CVD mortality.

Some limitations other than using BMI should be noted about the present study. Firstly we used non-fasting blood samples

and thus we might have misclassified participants with high blood glucose or hypertriglyceridemia. Secondly we did not adjust for socioeconomic status because relevant information was not available. However, all Japanese are covered by the national health insurance program and socioeconomic status does not affect access to treatment. Therefore, the impact of socioeconomic status on our findings should be minimal.

In conclusion, the CVD risk was obviously higher among individuals with, than without high blood glucose and multiple metabolic risk factors, suggesting that high blood glucose plays an important role in CVD mortality. Conversely, the prevalence of non-obese participants with several metabolic factors

was quite high and their CVD risk was high. Thus, metabolic factors should be carefully considered and appropriately managed even among individuals with a BMI below 25.

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Table 1. Means and prevalence of baseline characteristics of 2,999 men and 4,220 women aged 30 years and older (NIPPON DATA90, 1990).

Baseline risk characteristics	Number of metabolic factors					
	0	1	2	3	4	5
Number of participants	1604	2657	1643	942	336	37
Women (%)	67.3	54.3	59.4	55.4	56.9	56.0
Age (years)	44.1±11.0	52.7±13.6	56.0±13.4	56.1±12.5	58.0±13.2	58.6±11.2
BMI (kg/m ²)	20.9±2.0	21.9±2.4	24.1±3.2	25.5±3.1	26.7±2.4	27.8±2.0
Systolic Blood Pressure (mmHg)	114.9±8.8	137.2±19.7	141.8±19.0	145.8±17.4	149.2±16.4	154.3±18.4
Diastolic Blood Pressure (mmHg)	71.7±7.5	82.1±11.4	84.3±11.4	86.7±10.8	88.1±11.5	89.7±12.0
Total Cholesterol (mg/dl)	194.2±32.0	198.6±36.2	206.0±37.9	217.3±40.8	224.6±42.7	237.8±43.7
Triglycerides (mg/dl)	78(57-106)	95(70-127)	127(91-176)	192(131-252)	255(205-346)	269(214-363)
HDL-cholesterol (mg/dl)	63.5±12.8	58.2±14.6	49.5±13.2	42.4±10.9	37.5±7.8	36.2±6.8
Blood glucose (mg/dl)	92.6±13.5	98.4±22.5	105.5±33.0	114.4±45.9	126.5±51.3	196.7±69.7
High blood pressure (%)	0.0	72.1	82.8	93.7	99.4	100
High triglycerides (%)	0.0	2.8	20.0	55.1	89.3	100
Low HDL-cholesterol (%)	0.0	16.1	46.0	73.5	93.2	100
High blood glucose (%)	0.0	2.1	11.7	19.2	33.3	100
Drinking						
never-drinker (%)	73.8	64.0	70.9	66.8	73.8	73.0
ex-drinker (%)	2.3	2.7	3.4	3.8	3.3	10.8
current drinker (%)	23.9	33.3	25.7	29.4	22.9	16.2
Smoking						
never-smoker (%)	65.8	58.2	61.6	58.1	54.2	56.8
ex-smoker (%)	8.6	11.2	11.8	12.3	13.7	10.8
current smoker (%)	25.6	30.6	26.6	29.6	32.1	32.4
Physical activity						
yes (%)	18.9	20.3	20.6	21.2	19.3	24.3
no for physical problems (%)	3.4	5.3	6.8	7.1	9.0	10.8
no for other reasons (%)	77.7	74.4	72.6	71.8	71.7	64.9

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein cholesterol

Metabolic factors were defined as follows. Obesity (BMI \geq 25 kg/m²), High blood pressure (SBP \geq 130 mmHg and /or DBP \geq 85 mmHg and /or medication), High blood glucose (non-fasting blood glucose \geq 140 mg/dl and /or medication), High triglycerides (non-fasting triglycerides \geq 200 mg/dl and /or medication), Low HDL-cholesterol (HDL-cholesterol \leq 40 mg/dl (men), \leq 50 mg/dl (women)) Triglyceride value was shown in median and interquartile range.

Table 2. Multiple adjusted hazard ratios and 95% confidence intervals according to the individual components of metabolic risk factor in 2,999 men and 4,220 women aged 30 years and older (NIPPON DATA90, 1990-1999).

Component of metabolic factor	Number of participants	HR	95%CI
Obesity	1706	0.87	0.60-1.27
High blood glucose	579	1.45	0.99-2.14
High blood pressure	4530	2.07	1.21-3.52
High triglycerides	1259	1.42	0.95-2.11
Low HDL-cholesterol	2224	0.79	0.56-1.12

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein cholesterol; HR: hazard ratio; CI: confidence intervals

Hazard ratios were estimated by Cox proportional hazard model adjusted for sex, age, total cholesterol, smoking habits, drinking habits, physical activity and other components of metabolic factors. Metabolic factors were defined as follows. Obesity ($BMI \geq 25 \text{ kg/m}^2$), High blood glucose (non-fasting blood glucose $\geq 140 \text{ mg/dl}$ and /or medication), High blood pressure (SBP $\geq 130 \text{ mmHg}$ and /or DBP $\geq 85 \text{ mmHg}$ and /or medication), High triglycerides (non-fasting triglycerides $\geq 200 \text{ mg/dl}$ and /or medication), Low HDL-cholesterol (HDL-cholesterol $\leq 40 \text{ mg/dl}$ (men), $\leq 50 \text{ mg/dl}$ (women))

Table 3. Multiple adjusted hazard ratios and 95% confidence intervals according to number of metabolic factors in 2,999 men and 4,220 women aged 30 years and older (NIPPON DATA90, 1990-1999).

Number of metabolic factors	Number of participants	Person-years	Cardiovascular deaths	HR	95%CI
0	1604	15740	8	1.00	-
1	2657	25398	67	1.93	0.92-4.05
2	1643	15526	52	1.94	0.91-4.13
3	942	8999	29	2.12	0.96-4.70
4	336	3167	15	2.44	1.02-5.84
5	37	361	2	3.27	0.69-15.50
					P for trend = 0.074

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein cholesterol; HR: hazard ratio; CI: confidence intervals

Hazard ratios were estimated by Cox proportional hazard model adjusted for sex, age, total cholesterol, smoking habits, drinking habits and physical activity. Metabolic factors were defined as follows. Obesity ($BMI \geq 25 \text{ kg/m}^2$), High blood glucose (non-fasting blood glucose $\geq 140 \text{ mg/dl}$ and /or medication), High blood pressure ($SBP \geq 130 \text{ mmHg}$ and /or $DBP \geq 85 \text{ mmHg}$ and /or medication), High triglycerides(non-fasting triglycerides $\geq 200 \text{ mg/dl}$ and /or medication), Low HDL-cholesterol ($HDL\text{-cholesterol} \leq 40 \text{ mg/dl}$ (men), $\leq 50 \text{ mg/dl}$ (women))

Table 4. (A) Blood glucose category-specific multiple adjusted hazard ratios and 95% confidence intervals according to number of metabolic factors other than high blood glucose, (B) BMI category-specific multiple adjusted hazard ratios and 95% confidence intervals according to the number of metabolic factors other than obesity in 2,999 men and 4,220 women aged 30 years and older (NIPPON DATA90, 1990-1999).

	Number of metabolic factors	Number of participants	Person-years	Cardiovascular deaths	HR	95%CI	HR*	95%CI*	
(A) Without high blood glucose	0	1604	15740	8	1.00	-			
	1	2600	24867	65	1.91	0.91-4.02			
	2	1451	13796	45	1.99	0.93-4.28			
	3 and more	985	9522	22	1.61	0.71-3.67			
	With high blood glucose	0 and 1	249	2241	9	1.78	0.68-4.67		
		2	181	1638	12	3.67	1.49-9.03		
		3 and more	149	1367	12	3.25	1.31-8.06		
(B) BMI < 25 kg/m ²	0	1604	15740	8	1.00	-	1.00	-	
	1	2474	23576	67	1.98	0.94-4.17	2.14	0.85-5.43	
	2	993	9282	37	1.95	0.90-4.25	2.24	0.86-5.82	
	3 and more	442	4108	24	2.83	1.25-6.39	3.35	1.25-8.95	
	BMI ≥ 25 kg/m ²	0 and 1	833	8045	15	1.75	0.73-4.16	2.12	0.76-5.89
		2	551	5339	10	1.47	0.57-3.75	1.78	0.59-5.19
		3 and more	322	3080	12	2.37	0.96-5.89	2.84	0.99-8.17

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein cholesterol; HR: hazard ratio; CI: confidence interval

Hazard ratios were estimated by Cox proportional hazard model adjusted for sex, age, total cholesterol, smoking habits, drinking habits and physical activity.

(A) High blood glucose was defined non-fasting blood glucose ≥ 140 mg/dl and /or medication. Metabolic factors were defined as follows. Obesity (BMI ≥ 25 kg/m²), High blood pressure (SBP ≥ 130 mmHg and /or DBP ≥ 85 mmHg and /or medication), High triglycerides (non-fasting triglycerides ≥ 200 mg/dl and /or medication), Low HDL-cholesterol (HDL-cholesterol ≤ 40 mg/dl (men), ≤ 50 mg/dl (women)) In the group with high blood glucose, number 0 and 1 of metabolic factors were combined because we found only two cardiovascular deaths in the group whose number of metabolic factors was 0.

(B) HR* and 95%CI* were analyzed for participants BMI ≥ 18.5. Metabolic factors were defined as follows. High blood pressure (SBP ≥ 130 mmHg and /or DBP ≥ 85 mmHg and /or medication), High blood glucose (non-fasting blood glucose ≥ 140 mg/dl and /or medication), High triglycerides (non-fasting triglycerides ≥ 200 mg/dl and /or medication), Low HDL-cholesterol (HDL-cholesterol ≤ 40 mg/dl (men), ≤ 50 mg/dl (women)) In the group BMI ≥ 25, number 0 and 1 of metabolic factors were combined because we found no cardiovascular death in the group whose number of metabolic factors was 0.