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Retrospective Cohort Study for the Evaluation of Life-Style Risk Factors in Developing Metabolic Syndrome under the Estimated Abdominal Circumference

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Abstract

Metabolic Syndrome (MetS) has recently been receiving much attention in Japan. Though some earlier studies discussed the effects of eating behavior or physical activity in developing MetS, it is not clear which of them has the greater effect. The study population was 35,415 males (average age: 45.3 years old) who have had health checkups at a health care center established by one of the largest manufacturers in Japan during the period from 1995 to 2005. They are registered in the study cohort retrospectively using the year when their checkup result was first found in the record files during the period. The exposures are life-style risk factors identified by questionnaires submitted at the checkups and the event is to become diagnosed with MetS based on the estimated abdominal circumference and the diagnostic criteria proposed by 8 Japanese medical academic societies. The impact of each exposure on contributing to the event is examined based on hazard ratios developed by Cox's proportional hazard model. After adjusting for age and family history by multivariate analysis, the hazard ratios of "slow eating: no" to "yes" is 1.228 ($p<0.001$), "sedentary work" to "standing work, etc" 1.195 ($p<0.001$), "drinking: 3 times or more per week" to "less than 3 times" 1.094 ($p=0.003$), "sleeping: less than 6 hours" to "6 hours or more" 1.085 ($p=0.013$). The effects of eating behavior and physical activity are suggested to be almost the same at approximately 1.2, and those of drinking and sleeping hours appear to be less, at around 1.1.

Key words: metabolic syndrome, eating behavior, physical activity, drinking, sleeping, retrospective cohort study, Cox's proportional hazard model

❖ Background

As the number of patients with diabetes, hypertension and hyperlipidemia has been growing, Metabolic Syndrome (MetS) has increasingly received attention in Japan. In April, 2005, eight Japanese medical academic societies jointly proposed the diagnostic criteria for MetS (refer to Figure 1)[1].

It is generally and widely accepted that life-style habits have a close relationship with the development of MetS, and some earlier studies[1–5] discuss the effects of eating behavior or physical activity in developing MetS. However, it has not been clear which of them have a greater contribution. This study examines the impacts of life-style risk factors in developing MetS by retrospectively utilizing health checkup result data of 35,415 Japanese males for the period from 1995 to 2005.

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❖ Method

Study design

The study population was 53,094 subjects who

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Visceral fat accumulation

Abdominal circumference Male≧85 cm
Female≧90 cm
(equivalent to visceral fat square measure ≧100 cm^2 for both male or female)

in addition to the above, two or three of the followings

Triglyceride value ≧ 150 mg/dl
and/or
HDL cholesterol value < 40 mg/dl

Systolic blood pressure ≧ 130 mmHg
and/or
Diastolic blood pressure ≧ 85 mmHg

Fasting blood sugar ≧ 110 mg/dl

Figure 1. The diagnostic criteria for metabolic syndrome in Japan

* It is desirable to measure the amount of visceral fat by methods such as CT scans.
* The abdominal circumference should be measured at navel height with light breathing while standing. If there is obvious fat accumulation and the navel points downward, the circumference should be measured at mid-level between the subcostal edge and the anterior interspinal line.
* If an individual is diagnosed with metabolic syndrome, a glucose tolerance test is recommended, although not necessary, for the diagnosis.
* If an individual is receiving medication for hypertriglyceridemia, decreased blood HDL-C, hypertension, or diabetes, this should be noted as respective items.
* The existence of diabetes or hyperlipidemia is not excluded from the diagnosis of Metabolic Syndrome.

had health checkups at one of the health care centers (hereinafter called "the facility") established by Hitachi, Ltd., one of the largest manufacturers in Japan, during the period from 1995 to 2005. Subjects were registered in the study cohort retrospectively using the year when their checkup results were firstly found in the record files during the period (hereinafter called "first year"). The subjects (8,093 persons) who fell under the diagnostic criteria for MetS proposed by 8 Japanese medical academic societies (hereinafter called "the diagnostic criteria") in his/her first year are excluded from the study cohort. After excluding this group, the study cohort consisted of 45,001 subjects (35,415 males and 9,586 females). The observation was continued longitudinally from each subject's first year and terminated in the year when he/she first was diagnosed with MetS according to the diagnostic criteria. The observation was discontinued in the year when a subject's checkup results were not recorded.

Identification of the event

Although abdominal circumference measurement is necessary in order to diagnose MetS based on the diagnostic criteria, it was not measured at the facility before September 2005. This issue was handled by the following 2 strategies.

(1) Estimation of abdominal circumference in the past years

The facility did not start to measure abdominal circumference until September, 2005. Utilizing checkup result data that included abdominal circumference measurement during the period from September, 2005 to June, 2006 (11,156 males and 1,950 females), a regression analysis was performed using abdominal circumference as the dependent variable, and age, height, body weight, body fat percentage as independent variables. By inputting age, height, body weight, body fat percentage figures from the past years into the calculated regression expressions, abdominal circumference figures for the previous years were estimated.

The cutoff points of abdominal circumference shown in the diagnostic criteria (85 cm for male and 90 cm for female) are figures measured at standing position. But those recorded at the facility are figures measured at supine body position. In order to have cut-off points at supine body position, the second strategy below is employed.

(2) Cut-off point of abdominal circumference at supine body position

Since September, 2005, the facility has provided the opportunity for those who are interested to have a visceral fat square measure estimated by a computed tomography (CT) image at abdominal part with the image processing software (fatPointer). Utilizing the visceral fat square measure and checkup result data during the period from September, 2005 to June, 2006 (3,557 males and 567 females), cut-off points of abdominal circumference at supine body position which give 100 cm^2 of visceral fat square measure is analyzed. The result of this analysis was used, instead of the cut-off points shown in the diagnostic criteria, for establishing the diagnosis in this study.

Identification of risk factors

Life-style risk factors as statistical exposures were identified by questionnaires submitted at checkups in the subject's first year. The questionnaires have more than 50 questions in the areas of working habits,

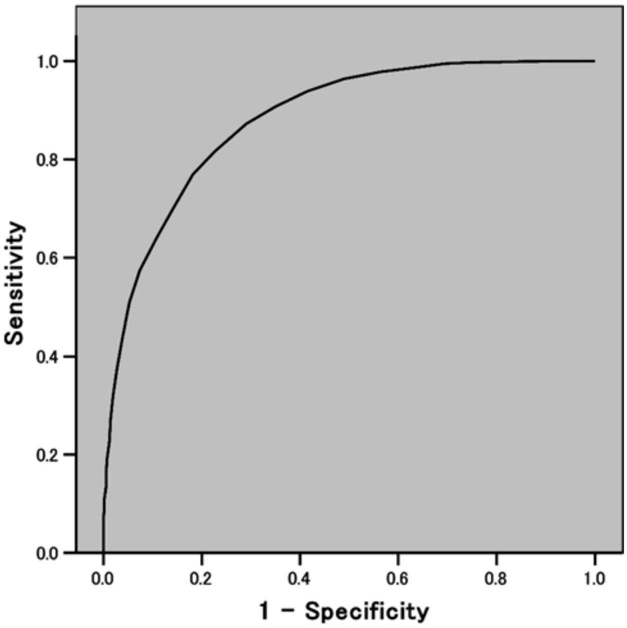

Figure 2. ROC curve of abdominal circumference at supine body position against 100 cm^2 of visceral fat square measure (3,557 males)

living conditions, smoking, drinking, eating behavior, physical activity, subjective symptom and history of disease including parents, brothers and sisters.

Statistical method

Receiver Operating Characteristic (ROC) analysis was used for the analysis of cut-off points of abdominal circumference at supine body position which yielded 100 cm^2 of visceral fat square measure. Multiple Regression analysis was used to generate regression expressions of abdominal circumference. The impact of each risk factor towards having the event was examined based on hazard ratios developed by Cox's proportional hazard model. The software for statistical analysis is SPSS version 14.0J for Windows.

Ethical review board

The Ethical Review Board of the Graduate School of Health Management, Keio University approved the protocol of this study.

❖ Results

Cut-off point of abdominal circumference at supine body position

The ROC curve of abdominal circumference at supine body position versus 100 cm^2 of visceral fat square measure for male is shown in Figure 2. The point of abdominal circumference at supine body position which gives the minimum distance from the coordinate (0,1) is 82.5 cm as shown in Table 1. Since the point is confirmed to be at almost the same level for each age band, under 40 years old, 40–49 years old, 50–59 years old and 60 years old and over, 82.5 cm of abdominal circumference at supine body position was used in this study instead of 85 cm of abdominal circumference at standing position showed in the diagnosis criteria.

The ROC curve of abdominal circumference at supine body position against 100 cm^2 of visceral fat square measure for female is shown as Figure 3. The point of abdominal circumference at supine body

Table 1. Sensitivity, specificity, etc of ROC curve (Male)

ACSBP*[1]	Sensitivity	1-Specificity	Distance from coordinate (0,1)
67.5	1.000	0.973	0.973
68.5	1.000	0.955	0.955
69.5	1.000	0.939	0.939
70.5	1.000	0.917	0.917
71.5	0.999	0.885	0.885
72.5	0.999	0.856	0.856
73.5	0.998	0.809	0.809
74.5	0.997	0.755	0.755
75.5	0.995	0.694	0.694
76.5	0.988	0.642	0.642
77.5	0.978	0.564	0.564
78.5	0.964	0.489	0.491
79.5	0.939	0.415	0.420
80.5	0.908	0.351	0.363
81.5	0.872	0.291	0.318
82.5	**0.816**	**0.227**	**0.292**
83.5	0.769	0.182	0.294
84.5	0.698	0.141	0.333
85.5	0.640	0.108	0.376
86.5	0.574	0.074	0.433
87.5	0.509	0.053	0.494
88.5	0.437	0.039	0.564
89.5	0.374	0.027	0.626
90.5	0.320	0.020	0.680
91.5	0.271	0.015	0.729
92.5	0.227	0.012	0.773
93.5	0.192	0.008	0.808
94.5	0.159	0.005	0.841
95.5	0.133	0.005	0.867

*[1]ACSBP: Abdominal Circumference at Supine Body Position.

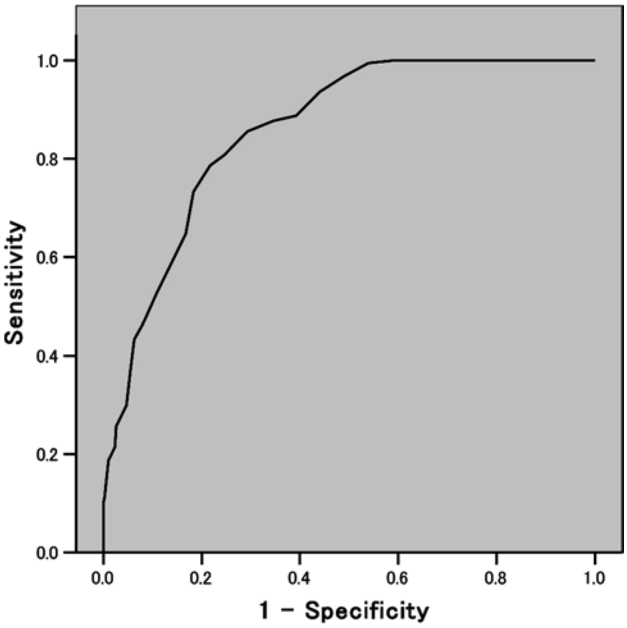

Figure 3. ROC curve of abdominal circumference at supine body position against 100 cm^2 of visceral fat square measure (567 Female)

position which gives the minimum distance from the coordinate (0,1) is also 82.5 cm as shown in Table 2.

Regression expression of abdominal circumference

Utilizing checkup result data with abdominal circumference measurement during the period from September, 2005 to June, 2006 (11,156 males and 1,950 females), regression expressions to calculate abdominal circumference as a dependent variable, based on age, height, body weight, body fat percentage (by impedance method) as independent variables are as follows. Since body fat measures were only available in 42% of checkup records, regression expressions with and without body fat percentage were both analyzed.

(1) Male

In cases where body fat percentage was available:

Abdominal Circumference (cm)

= 56.873 + 0.644*weight (kg) – 0.199*height (cm) + 0.150*age (years old) + 0.419*body fat percentage (%)

Squared multiple correlation coefficient adjusted for the degrees of freedom: 0.865

In cases where body fat percentage was not available:

Abdominal Circumference (cm)

= 81.163 + 0.829*weight (kg) – 0.356*height (cm) + 0.132*age (years old)

Table 2. Sensitivity, specificity, etc of ROC curve (Female)

ACSBP*[1]	Sensitivity	1-Specificity	Distance from coordinate (0,1)
74.5	1.000	0.592	0.592
75.5	0.995	0.539	0.539
76.5	0.968	0.490	0.491
77.5	0.936	0.440	0.444
78.5	0.888	0.393	0.408
79.5	0.877	0.346	0.367
80.5	0.856	0.293	0.327
81.5	0.807	0.246	0.312
82.5	**0.786**	**0.217**	**0.305**
83.5	0.733	0.183	0.324
84.5	0.647	0.168	0.391
85.5	0.572	0.131	0.447
86.5	0.524	0.107	0.488
87.5	0.471	0.084	0.536
88.5	0.433	0.063	0.570
89.5	0.369	0.055	0.633
90.5	0.299	0.047	0.702
91.5	0.257	0.026	0.744
92.5	0.214	0.024	0.786
93.5	0.187	0.010	0.813
94.5	0.139	0.005	0.861
96.0	0.112	0.003	0.888
97.5	0.102	0.000	0.898
98.5	0.075	0.000	0.925
99.5	0.053	0.000	0.947
100.5	0.043	0.000	0.957

*[1]ACSBP: Abdominal Circumference at Supine Body Position.

Squared multiple correlation coefficient adjusted for the degrees of freedom: 0.844

(2) Female

In cases where body fat percentage was available:

Abdominal Circumference (cm)

= 38.449 + 0.604*weight (kg) – 0.110*height (cm) + 0.184*age (years old) + 0.509*body fat percentage (%)

Squared multiple correlation coefficient adjusted for the degrees of freedom: 0.823

In cases where body fat percentage was not available:

Abdominal Circumference (cm)

= 75.615 + 0.965*weight (kg) – 0.378*height (cm) + 0.170*age (years old)

Squared multiple correlation coefficient adjusted for the degrees of freedom: 0.804

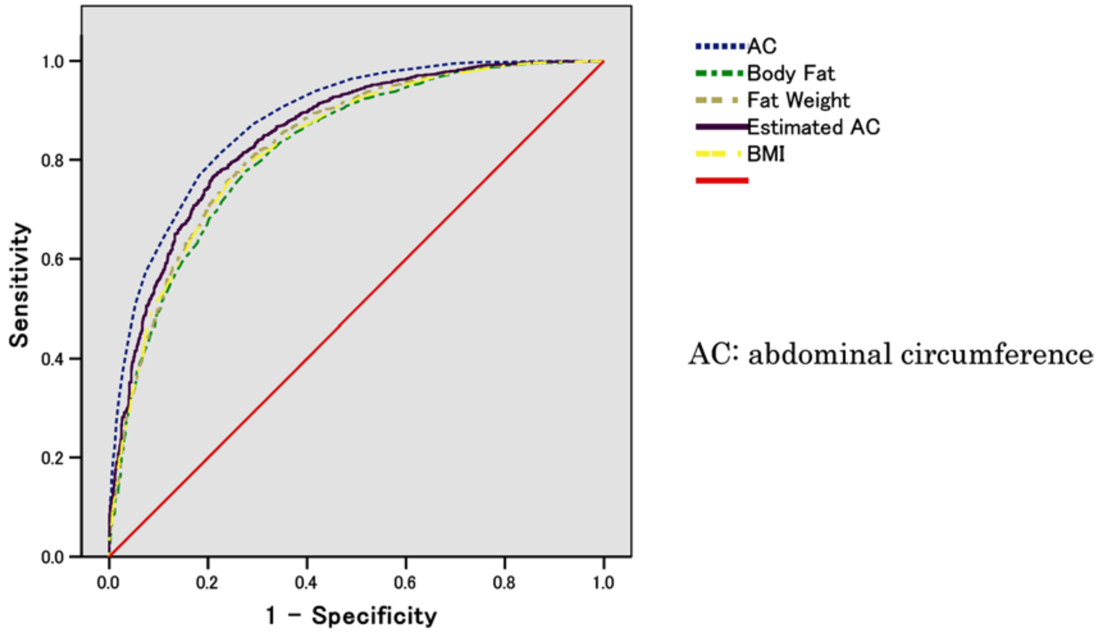

Figure 4. ROC curves of abdominal circumference at supine body position and other indicators against 100 cm^2 of visceral fat square measure (Male)

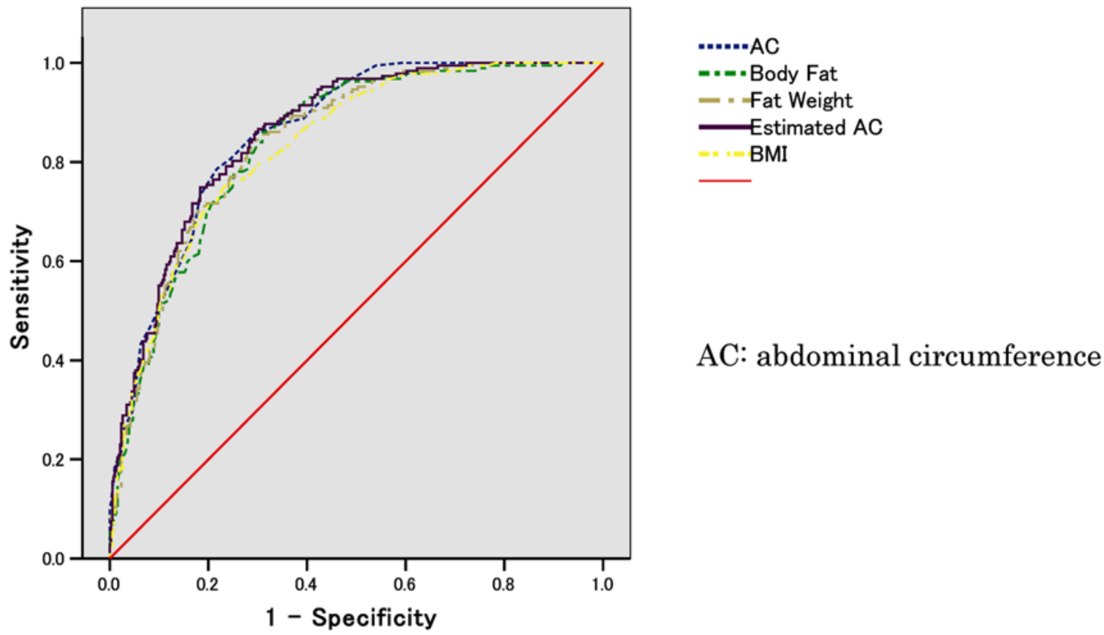

Figure 5. ROC curve of abdominal circumference at supine body position and other indicators against 100 cm^2 of visceral fat square measure (Female)

Evaluation of regression expression

The ROC curves of the estimated abdominal circumference as well as BMI, body fat percentage and fat weight with the measured abdominal circumference for male and female are shown in Figure 4 and Figure 5 respectively. It is clear that the estimated abdominal circumference is a better indicator for the 100 cm^2 of visceral fat square measure than were BMI, body fat percentage or fat weight, since the curve of the estimated abdominal circumference lies upward and to the left of those other indices.

Table 3. Percentage of MetS by health checkup year (Male)

Male	Year									
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
No. of Subjects	9,091	11,279	14,392	20,276	20,700	27,120	25,748	25,149	24,946	25,310
MetS	1,514	2,092	2,820	4,157	4,357	5,538	5,341	5,361	5,409	5,543
Non-MetS	7,577	9,187	11,572	16,119	16,343	21,582	20,407	19,788	19,537	19,767
% of MetS	**16.7%**	**18.5%**	**19.6%**	**20.5%**	**21.0%**	**20.4%**	**20.7%**	**21.3%**	**21.7%**	**21.9%**
Ave. Age	45.8	46.7	47.8	49.5	50.2	48.9	48.5	48.3	47.4	48.5

Table 4. Percentage of MetS by health checkup year (Female)

Female	Year									
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
No. of Subjects	3,231	3,581	3,491	4,086	3,538	4,259	4,302	4,390	4,316	4,472
MetS	210	262	244	278	225	267	286	288	302	308
Non-MetS	3,021	3,319	3,247	3,808	3,313	3,992	4,016	4,102	4,014	4,164
% of MetS	**6.5%**	**7.3%**	**7.0%**	**6.8%**	**6.4%**	**6.3%**	**6.6%**	**6.6%**	**7.0%**	**6.9%**
Ave. Age	48.4	43.4	47.3	47.7	48.1	48.8	49.3	48.9	48.8	48.8

Table 5. The structure of the study cohort (Male)

First Year	No. of Subjects	MetS	Non-MetS			Ave. Age at First
			Total	Complete	Censored	
1995	6,135	1,209	4,926	1,291	3,635	42.2
1996	3,737	519	3,218	568	2,650	47.4
1997	3,043	429	2,614	570	2,044	46.9
1998	3,659	562	3,097	649	2,448	47.5
1999	5,254	875	4,379	1,091	3,288	50.2
2000	1,637	127	1,510	356	1,154	45.8
2001	7,182	1,139	6,043	3,040	3,003	46.6
2002	1,957	161	1,796	766	1,030	38.9
2003	1,442	102	1,340	612	728	38.1
2004	1,369	58	1,311	753	558	36.0
Total	**35,415**	5,181	30,234	9,696	20,538	**45.3**

Cohort characteristics

With the estimated abdominal circumference of 82.5 cm as a cut-off point, the numbers of subjects with MetS for each health checkup year for male and female are shown in Table 3 and Table 4, respectively. In recent years, the percentage of males with MetS has grown from 16 to 21% of male subjects, whereas the rate in females has been stable at around 7%, one third the current rate of males. Accordingly, the remainder of the analysis was conducted only for males.

Since subjects who fall under the diagnostic criteria for MetS in their first year were excluded from the study cohort, the structure of the male cohort is as shown in Table 5.

Univariate analysis

The result of univariate analysis by Cox's proportional hazard model of the years free from MetS with life-style risk factors is as shown in Table 6. The factors which are statistically significant are smoking,

Table 6. The result of univariate analysis by Cox's proportional hazard model

	Life-Style Factors	Remarks	p	exp (β)
Sleeping	average sleepng hours in the last month	1: less than 6 hours, 2: 6 hours or more[ref]	0.339	
Overtime	Average overtime work per month	1: less than 60 hours [ref], 2: 60 hours or more	0.132	
Smoking	**Smoking**	1: No [ref], 2: Quitted, 3: Yes	**0.006**	2/1 1.089 3/1 0.957
Drinking	**No. of times drinking per week**	1: less than 3 times [ref], 2: 3 times or more	**<0.001**	1.124
Eating	**breakfast everyday**	1: seldom or never 2: sometimes, everyday [ref]	**0.011**	0.884
	# of dinners after 9PM per week	0: None[ref], 1: One or more	0.642	
	Breakfast, lunch:>=15 minutes Dinner: >=20 minutes	1: Yes[ref], 2: No	**<0.001**	1.151
Physical Activity	commutation	1: On foot, 2: Train bus, car, bike [ref]	0.083	
	Walking on commutation	1: less tha 20 minutes [ref], 2: 20 minutes or more	0.868	
	Physical Activity and walking on work	1: sedentary work [ref] 2: standing work, a lot of walk, heavy physical labor, etc.	**<0.001**	0.864
	Physical Activity volume per month	Mets*hour/month	0.123	
	# of LTPA per month	0: None [ref], 1: less than 8 times, 2: 8 times or more	0.227	
Family History	**hypertension**	0: No [ref], 1: Yes	**<0.001**	1.354
	diabetes	0: No [ref], 1: Yes	**<0.001**	1.178
	hyperlipidemia	0: No [ref], 1: Yes	**0.040**	1.282
	chronic hepatitis, cirrhosis	0: No [ref], 1: Yes	0.817	
	cancer	0: No [ref], 1: Yes	0.058	
	stroke	0: No [ref], 1: Yes	**<0.001**	1.222
	angina, myocardial infarction	0: No [ref], 1: Yes	**0.001**	1.183

Note: exp (β) is hazard ratio and [ref] means reference. "2/1" in the Smoking row means the ratio of the hazard of choice 2 against that of choice 1.

drinking, breakfast, slow eating (15 minutes or more for breakfast and lunch, and 20 minutes or more for dinner), physical activity at work, family history of hypertension, diabetes, hyperlipidemia, stroke and angina/myocardial infarction.

Multivariate analysis

The result of multivariate analysis by Cox's proportional hazard model is as shown in Table 7. The analyzed subjects are 31,153 males who were employees of this manufacturing company, neither retired nor family members of the employees in his first year as a result of including "Physical activity at work" as a covariate. Sleeping, which is not statistically significant in the univariate analysis, is significant in this multivariate analysis when introducing age as a covariate. Smoking, eating breakfast everyday, family history of hyperlipidemia or angina/myocardial infarction were not significant. The hazard ratios of "slow eating: no" to "yes" is 1.228 (p<0.001), "sedentary work" to "standing work, etc" 1.195 (p<0.001), "drinking: 3 times or more per week" to "less than 3 times" 1.094 (p=0.003), "sleeping: less than 6 hours" to "6 hours or more" 1.085 (p=0.013). In summary, the effects of eating behavior and physical activity are suggested to be almost the same at around 1.2 and those of drinking and sleeping hours are to be less at around 1.1.

The results of the analysis are unchanged by both the step-up and step-down procedure. The proportionality of hazard is confirmed by time-dependent Cox regression analysis.

❖ Discussion

It is generally and widely accepted that life-style habits have a close relationship with the development

Table 7. The result of multnivariate analysis by Cox's proportional hazard model

	Variables	Remarks	exp(β)	p-value	95% CI of exp(β)	
					lower	upper
X_1	Sleeping	"<6 hours" vs ">=6hours" [ref]	1.085	0.013	1.017	1.157
X_2	Drinking	"<3 times/week" [ref] vs ">=3"	1.094	0.003	1.030	1.162
X_3	Slow Eating	"Yes" [ref] vs "No"	1.228	<0.001	1.130	1.335
X_4	Physical Activity on work	"Sedentary work" vs "Standing work, etc" [ref]	1.195	<0.001	1.124	1.270
X_5	Family History Hypertension	"No" [ref] vs "Yes"	1.290	<0.001	1.211	1.374
X_6	Family History Diabetes	"No" [ref] vs "Yes"	1.117	0.010	1.027	1.215
X_7	Age	Age at First Year: years old	1.022	<0.001	1.019	1.026

"Slow Eating: Yes" means to spend 15 minutes or more for breakfast & lunch, and 20 minutes or more for dinner. "No" means to spend less than this time for at least one of the three meals.

Table 8. Base-line characteristics of checkup results in his first year

		MetS	Non-MetS	Censored
n		5,181	9,696	20,538
Age		46.69 ± 8.68	42.68 ± 8.01	46.26 ± 11.58
Hight	cm	168.90 ± 6.20	169.42 ± 6.18	167.90 ± 6.57
Weight	kg	70.36 ± 8.14	63.44 ± 8.37	63.17 ± 8.79
BMI	kg/m^2	24.64 ± 2.22	22.08 ± 2.43	22.38 ± 2.56
SBP	mmHg	125.68 ± 14.49	117.54 ± 13.97	119.83 ± 14.98
DBP	mmHg	78.55 ± 9.85	72.55 ± 9.58	74.20 ± 10.10
TG	mg/dl	144.49 ± 96.20	111.99 ± 76.38	115.41 ± 80.17
HDL-C	mg/dl	51.78 ± 12.89	57.57 ± 14.43	57.22 ± 14.81
FBS	mg/dl	105.80 ± 15.22	101.30 ± 13.77	103.17 ± 16.75

Average ± STD.

of MetS. The life-style risk factors themselves showed in this study, drinking behavior, eating behavior, physical activity, family history of hypertension and/or diabetes, etc. are the usual ones. Some earlier studies showed in Background discuss the effect of eating behavior or physical activity in developing MetS, however, it has not been clear which of them have a greater contribution. This study shows first time ever the comparison of the contributions of risk factors, especially the one of eating behavior aspect and the one of physical activity aspect. As stated above, on a hazard ratio basis, the effects of eating behavior and physical activity are suggested to be almost the same at around 1.2 and those of drinking and sleeping hours to be less, at around 1.1. The strengths of this study are 1) the large size of the study cohort, 2) examining the longitudinal relationship of the exposures and the diagnostic event, and 3) retrospective cohort design by way of the estimation of abdominal circumferences in the past years. The limitations of this study are as follows.

As shown in Table 5, the cohort contains about 20,000 censored cases, which makes the observation period rather short, average 3.41 years, median 2 years. Since the analyses include censored cases, it is considered that the over estimation of the occurrence of the event during the period of a few years just after the first year could be kept off. But the method implies the assumption that the occurrence level of the event for the censored cases after censored is about the same as that for the complete cases. The validity of this assumption should be carefully examined. One consideration based on the base-line characteristics of checkup results among groups as shown in Table 8 is as follows.

Comparing the group of subjects who have fallen under the diagnosis criteria during the observation period (MetS group) against the group who have not (non-MetS group), the average of MetS group is older in age, shorter in height, heavier in weight, higher in

BMI, SBP, DBP, TG and FBS, and lower in HDL-C than that of non-MetS group respectively. Though the life-style risk factors are identified by the questionnaires in the first year, the life-styles are supposed to have been maintained through the past years before the first year. Therefore, it could possibly be inferred that the life-style risk factors have acted upon the checkup results in the first year.

The average of censored group lies midway between MetS group and non-MetS group except weight and the standard deviation of censored group is larger than those of MetS group and non-MetS group except TG. Therefore, Sensor group is supposed to be a mixture of subjects who have either of the characteristics of MetS or non-MetS, and not to be heavily disproportionately biased to either of MetS or non-MetS.

The subjects of this study are mainly older than 35 years of age and the average age is 45.3 years old. The generalizability of the result to people under 35 years of age should be carefully examined. As the subjects are employees, retired and family members of one company group and located in a rather small area in north Kanto, Japan, the life-styles based on the locality, the industry and the working practice, etc. might be rather homogeneous or not sufficiently dispersed. The generalizability of the result to people in other localities, industries or working practices, etc. should be carefully examined.

Furthermore, the questionnaires used in this study are not designed specifically for the study, and it is not improbable that the questionnaires did not sufficiently highlight the impactable life-style risk factors for developing MetS. In that sense, the statement that the factors which did not show statistical significance in this study have no impact in developing MetS is considered to be too strong.

❖ Acknowledgements

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❖ Note

[1] The eight academic societies are the Japan Society for the Study of Obesity, the Japan Atherosclerosis Society, the Japan Diabetes Society, the Japanese Society of Hypertension, the Japanese Circulation Society, the Japanese Society of Nephrology, the Japanese Society on Thrombosis and Hemostasis, the Japanese Society of Internal Medicine.