Increased Cardiovascular Mortality in Subjects with Metabolic Syndrome Is Largely Attributable to Diabetes and Hypertension in 159,971 Korean Adults

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Abstract

Context: Metabolic syndrome (MetS) is a risk factor for cardiovascular disease (CVD) mortality.

Objective: To evaluate the association of metabolic syndrome (MetS) with all-cause and cardiovascular mortality in apparently healthy young Korean subjects.

Design: A retrospective study of 155,971 participants (mean age 41.8 years) in a health screening program, followed up for 3.7 years (597628.2 person-years). The risk for all-cause mortality and cardiovascular disease (CVD) mortality were analyzed according to the presence or absence of MetS.

Main Outcomes: A total of 542 subjects died during follow-up. Women with MetS showed a significantly increased age-adjusted hazard ratio (HR) for all-cause mortality compared with women without MetS, even after adjustment for confounding factors (HR 1.82; 95% CI 1.15-2.88). Subjects with MetS showed a significantly increased risk for CVD mortality compared with those without MetS, even after adjustment for confounding factors (HR 1.60; 95% CI 1.02-2.20), of which significance disappeared when subjects with diabetes or hypertension at baseline were excluded from the analysis (HR 0.95; 95% CI 0.29-3.12).

Conclusions: The presence of MetS increased the risk for all-cause mortality in women and the risk for CVD mortality in total population. These increased HR attributed to the pre-existing diabetes or hypertension in this population.

Introduction

Metabolic syndrome (MetS) is a clustering of cardiometabolic risk factors (hyperglycemia, hypertension, dyslipidemia, and systemic inflammation) linked to insulin resistance and visceral obesity (1). The prevalence of metabolic syndrome varies from 5% to 41%, according to ethnic group. Since 1988, when Gerald Reaven first described MetS as "Syndrome X," an abundance of research has been undertaken on its pathophysiology, prognosis, implications, therapeutic strategies, and clinical relationships with other metabolic diseases (2).

Experts have focused on metabolic syndrome during the last few decades not only because of the increasing importance of obesity in the development of metabolic diseases but also because of the impact of MetS on mortality and the development of cardiovascular diseases (3,4). The presence of metabolic syndrome is associated with increased risk of diabetes the risk of diabetes by two-fold, coronary artery disease by two- to three-fold, and ischemic stroke by two-fold. MetS increases the risk for other metabolic diseases as well (1,4). There are conflicting data on the association between metabolic syndrome and mortality, with some studies showing an increase in mortality (3-7) and others showing no increase in mortality (8,9).

The definition of MetS has evolved during the three decades since the first description of "Syndrome X" by Reaven (2). MetS has been defined by taking into account insulin resistance, central obesity, and atherosclerosis (10). In 2009, members from the International Diabetes Federation; National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society and the International Association for the Study of Obesity produced a harmonized definition of MetS (11). In this definition, three abnormal findings out of five previously used components of

MetS qualify a person for MetS, with population- and country-specific definitions for waist circumference.

Most of the previously published studies that have investigated the relationships between MetS and mortality have been undertaken with subjects with a history of diabetes or hypertension included in the study population, since diabetes and hypertension qualify as individual components of the MetS definition. However, diabetes and hypertension may also be considered outcomes or endpoints of MetS (11). In addition, few studies have been performed on the association of MetS and mortality in Asian people. Therefore, we analyzed the all-cause and CVD mortality rates attributable to MetS before and after excluding subjects with diabetes or hypertension in a large number of Korean adults without previous history of CVD followed up with for a median of 3.7 years.

Subjects and Methods

Study population

The study population consisted of examinees who participated in a comprehensive health screening program at Kangbuk Samsung Hospital, Seoul, Korea (Kangbuk Samsung Health Study), from 2002 to 2009 (N=278,528). The purpose of the screening program was to promote health through early detection of chronic diseases and their risk factors. Additionally, in Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. About 60% of the participants were employees of various companies and local governmental organizations and their spouses, with the remaining participants registering individually for the program.

For this analysis, 119,347 were excluded for one or more of the following reasons: 136 subjects with missing data on metabolic syndrome components; 2,627 subjects with histories of malignancy; 97 subjects with history of coronary heart disease or ischemic stroke; 11 subjects with unknown vital status; and 116,605 subjects without waist circumference at baseline. As some individuals met more than one criterion for exclusion, the total number of eligible subjects for the study was 159,971. Further analyses were undertaken after excluding subjects with diabetes (n=7,292) and subjects with diabetes or hypertension (n=34,152).

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent, as we only accessed data retrospectively that was de-identified.

Mortality follow-up between January 1, 2002, and December 31, 2009, was based on the nationwide death certificate data of the Korea National Statistical Office. Deaths among subjects were confirmed by matching the information to death records. Death certificates

from the National Statistical Office were identified with the use of identification numbers assigned to subjects at birth. Abstractors coded the causes of death according to the International Classification of Diseases, 10th revision.

Anthropometric and laboratory measurements

Data on medical history, medication use, and health-related behaviors were collected through a self-administered questionnaire, while the physical measurements and serum biochemical parameters were measured by trained staff, all collected during the health examinations. Details regarding alcohol use included the frequency of intake per week and the average amount of intake per episode. Current smokers were identified and the weekly frequency of moderate- or vigorous-intensity physical activity assessed. Body weight was measured in light clothing and no shoes to the nearest 0.1 kilogram using a digital scale. Height was measured to the nearest 0.1 centimeter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Trained nurses measured sitting blood pressure with standard mercury sphygmomanometers. The waist circumference (WC) was measured in the standing position, at the middle point between anterior iliac crest and lower border of rib by a single examiner.

Blood specimens were sampled from the antecubital vein after more than 12 hours of fasting. Serum levels of glucose, uric acid, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein cholesterol (HDL-C) were measured using Bayer Reagent Packs (Bayer Diagnostics, Leverkusen, Germany) on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany).

Definitions of metabolic parameters

Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-report history of hypertension, or current use of antihypertensive medication (12). Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dL, a self-reported history of diabetes, or current use of diabetic medication (13).

MetS was defined based on the 'harmonized criteria' by the related federations (11). The cutoffs for the presence of abdominal obesity is defined as a WC ≥90 cm for men and ≥85 cm for women in Korea by ethnicity-specific cutoff (14)

Statistical analysis

The χ^2-test and Student's t-test were used to compare the characteristics of the study participants at baseline between alive and dead. The distribution of continuous variables was evaluated and the appropriate transformations were undertaken during analysis, as needed.

We used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals for mortality, comparing subjects with or without MetS, according to number of MetS components. The models were initially adjusted for age and sex, then for smoking status, alcohol intake, and regular exercise. Additional step-wise regression analyses with individual components of metabolic syndrome included in the model were performed as crude, and after adjustment for confounding variables. For testing linear risk trends, we used the number of categories as a continuous variable in the regression models. We checked the proportional hazards assumption by examining graphs of estimated log (-log) survival.

The statistical analysis was performed using STATA version 11.2 (StataCorp LP, College

Station, TX, USA). All reported P values are two tailed, and *P* value <0.05 was considered statistically significant.

Results

Mean age of total study population was 41.8 years with 597628.3 person-years and mean BMI was 23.5 kg/m^2. General characteristics of the participants at baseline are presented in Table 1. The proportion of subjects with MetS at baseline was 12.6%.

Risks for all-cause mortality according to presence or absence of MetS

During the median follow-up period of 3.7±2.2 years, 542 subjects died. When HR for all-cause mortality was analyzed, subjects with MetS did not show significantly increased HR compared with those without MetS (HR 1.19; 95% CI 0.98-1.46). When the analyses were performed separately for each sex, men did not show an increased HR for all-cause mortality in subjects with MetS (Table 2). In contrast, women showed significantly increased age-adjusted and multivariate HR for all-cause mortality (HR 1.82; 95% CI 1.15-2.88) (Table 2). When these analyses were performed after exclusion of subjects with diabetes or hypertension from the study population, there were no significant increases in HRs in either gender (Table 2).

Risks for all-cause mortality according to the number of MetS components

When risks for all-cause mortality were analyzed according to the number of MetS components at baseline, HR did not show any increasing trend from one to five components of MetS (Tab1e 3). Men did not show a significantly increased HR for all-cause mortality, while women showed a trend for increased HR for all-cause mortality as the number of MetS components increased (Table 3). When subjects with diabetes or hypertension at baseline

were excluded from the analyses, these results became non-significant.

Risks for cardiovascular mortality according to presence or absence of MetS

When risks for CVD mortality were analyzed according to the presence of absence of MetS, subjects with MetS showed significantly increased HR of 1.60 (95% CI 1.02-2.20) compared with subjects without MetS in the multivariate model (Table 4). Men showed a significantly increased multivariate HR for CVD mortality, while women did not show a significantly increased risk for CVD mortality. As observed for all-cause mortality, when subjects with diabetes or hypertension were excluded from the analyses, these HRs were not significantly different from subjects without MetS.

Risks for cardiovascular mortality according to the number of MetS components

When risks for CVD mortality were analyzed according to the number of MetS components at baseline, the HR linearly increased from 1.99 with one component of MetS to 2.98 in subjects with equal to or more than four components of MetS in the multivariate model (Table 5). Men showed a significant linear increase in the HR as the number of MetS components increased, whilst women did not (Table 5). When subjects with diabetes or hypertension were excluded from the analyses, the HRs were not significantly different from subjects without MetS.

Risks for all-cause mortality according to the individual components of MetS at baseline

When risks for all-cause mortality were analyzed according to the individual components of

MetS, the presence of high fasting blood glucose showed the highest HR among the individual components (HR 1.40; 95% CI 1.16-1.69) (Table 6). In stepwise multivariate model, the presence of high fasting blood glucose or high blood pressure showed significantly increased HRs for all-cause mortality (Table 6). However, when subjects with diabetes were excluded from the population, presence of high blood pressure and low triglyceride (TG) showed increased HRs for all-cause mortality. When subjects with diabetes or hypertension were excluded from the population, only presence of low TG level showed significantly increased HR for all-cause mortality, although this significance disappeared in multivariate model (Table 6).

Risks for CVD mortality according to the individual components of MetS at baseline

When risks for CVD mortality were analyzed according to the individual components of MetS, the presence of high blood pressure showed the highest HR among the individual components (HR 2.87; 95% CI 1.83-4.50) (Table 7). In stepwise multivariate model, only the presence of high blood pressure showed significantly increased HR for CVD mortality (Table 7). When subjects with diabetes were excluded from the population, only the presence of high blood pressure showed significantly increased HR for CVD mortality, which was consistently significant in stepwise multivariate model. When subjects with diabetes or hypertension were excluded from the population, none of the individual components showed significantly increased HR for CVD mortality (Table 7).

Discussion

In this study, our results show that, in a large number of Koreans participating in a health screening program followed for a median of 3.7 years, risks for all-cause mortality increased in women with MetS compared with those without MetS. However, these significant increases in HR disappeared when subjects with diabetes or hypertension were excluded from the study. For CVD mortality, HR was significantly increased in subjects with MetS even after adjustment for confounding variables, but the increased hazard was markedly attenuated after excluding subjects with diabetes or hypertension. The presence of individual components of MetS increased the HR for all-cause and CVD mortality, which disappeared after exclusion of subjects with diabetes or hypertension from the analyses. These results suggest that it is pre-existing diabetes or hypertension that largely accounts for the increased all-cause and CVD mortality attributable to MetS.

MetS is a cluster of risk factors for cardiometabolic diseases comprising abdominal obesity, hyperglycemia, high blood pressure, high TG, and low HDL-C (1). Numerous definitions of MetS have been proposed and many studies have been published regarding the clinical implications of MetS for metabolic or cardiovascular diseases. The main pathophysiological mechanism that has been proposed for how MetS contributes to these diseases involves insulin resistance, caused by accumulation of visceral fat. Overall, MetS is known to cause an approximately two-fold increase in risk of CVD over 5 to 10 years, and at least a five-fold increase in the development of diabetes (1). Importantly in the context of our findings, in the ‘harmonized definition of MetS recommended in 2009, the presence of diabetes or hypertension is included as one of the component features of the syndrome (11).

In this study, the presence of MetS increased the HR for all-cause in women and CVD mortality by 1.6- to 1.9-fold, but this increase in HR was attenuated, when subjects with

diabetes or hypertension were excluded from the analyses. Previously published studies show inconsistent results regarding the association between MetS and mortality, with some studies showing significantly increased risks for mortality in subjects with MetS (3-7) and others showing no increase in mortality in those with MetS (8,9). However, some of these studies included subjects with diabetes as a MetS criterion (5,6,8), while other studies excluded subjects with diabetes from the analyses (4,7,9). In a study by Ford et al. (8), which analyzed the risk for mortality in subjects with MetS, subjects with diabetes at baseline were excluded. The authors found that the presence of MetS was not associated with increased all-cause or CVD mortality. However, in a few studies, the presence of MetS was associated with an increased risk of mortality after exclusion of subjects with diabetes at baseline (4,7), which is in contrast to the results of our study. These data and our results suggest that the definition of MetS markedly affects the mortality risk, since diabetes *per se* increases the risk of CVD (15).

When the risks for all-cause and CVD mortality were analyzed according to the presence of individual components of MetS, the presence of high blood pressure showed consistently increased HRs for all-cause and CVD mortality in multivariate model. These significant effect of high blood pressure on increased mortality in subjects with MetS was consistent even after excluding subjects with diabetes. These results suggest relatively more important contribution of high blood pressure on increased mortality in subjects with MetS compared with other components of MetS. However, these effects disappeared after excluding subjects with hypertension from the model, meaning that the increased HR for mortality by the presence of MetS attributes largely to the effect of pre-existing hypertension.

There have been few studies investigating the association between MetS and mortality risk in Asian subjects. In a study of 25,471 Japanese men, MetS was associated with an increased risk of all-cause death with an HR of 4.88 (7). In that study, the investigators excluded

subjects with diabetes, hypertension, or CVD from the analyses, similar to our study, and they still showed an increased risk for mortality. Therefore, the discrepancy between our study data and the results of previous studies are not likely to be due to ethnic differences between Asians and people of white European ethnicity.

Our study has limitations. It was performed in a relatively homogenous population of working individuals who participated in a health screening program, and is not fully representative of the whole Korean population. In addition, our study was not an actually prospective or randomized controlled study, but was a longitudinal, observational study analyzed from a retrospective data. Therefore, direct cause-and-effect relationship could not be drawn from our study. However, the number of subjects included in our study is larger than in any previous studies investigating this question (4). Despite these limitations, our results give meaningful information to the literature regarding the association of increased mortality in Asian subjects with MetS.

We observed an increased risk for all-cause and CVD mortality in subjects with MetS with a median follow-up of 3.7 years in this large group of Korean adults without previous history of CVD. However, these increased HRs were attenuated after exclusion of subjects with diabetes or hypertension from the study population. These results suggest that it is diabetes or hypertension that largely accounts for the increased CVD mortality attributed to MetS.

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Table 1. General characteristics of the participants at baseline

Characteristics (n=159,971)	Alive (n=159,429)	Dead (n=542)	*P* value
Total population (%)	159,429 (99.7)	542 (0.3)	
Male (n=88,809)	88,395(55.4)	414 (76.4)	<0.001
Female (n=71,162)	71,034 (44.6)	128 (23.6)	
Age (years)	41.7 (10.1)	53.4 (13.0)	<0.001
BMI	23.5 (3.1)	23.8 (3.1)	0.0231
Waist circumference (cm)	79.8 (9.5)	83.4 (9.1)	<0.001
Systolic BP (mmHg)	115.0 (15.0)	124.6 (19.1)	<0.001
Diastolic BP (mmHg)	75.0(10.1)	79.1(11.8)	<0.001
Fasting blood glucose (mg/dl)	94.7 (17.7)	105.5 (34.0)	<0.001
Total cholesterol (mg/dl)	194.9 (34.8)	200.5 (40.6)	0.0002
LDL-C (mg/dl)	113.4 (30.0)	117.0 (34.0)	0.0060
HDL-C (mg/dl)	55.7 (12.7)	55.2 (14.4)	0.3604
Triglycerides (mg/dl)	105(73-155)	119(87-169)	<0.001
Smoking status (%)			<0.001
Never smoker, n=147,502	87,589 (55.9)	190 (36.2)	
Former smoker, n=45,921	27,443 (17.5)	133 (25.3)	
Current smoker, n=77,361	41,560 (26.5)	202 (38.5)	
Alcohol drinking status (%)			<0.001
No alcohol intake (0g/day), n=107,337	62,302 (40.0)	203 (38.8)	
Alcohol intake (10g/day), n=123,561	70,497 (45.2)	197 (37.7)	
Alcohol intake (20g/day), n=36,983	23,063 (14.8)	123 (23.5)	
Metabolic syndrome (%)	19,969 (12.5)	134 (24.7)	<0.001
Regular exercise (%)[a]	28,828 (18.3)	96 (18.1)	0.922
Education[b]	60,638 (70.2)	198 (48.2)	<0.001
History of hypertension (%)	14,167 (8.9)	117 (21.6)	<0.001
History of diabetes (%)	4,618 (2.9)	76 (14.0)	<0.001

Diabetes (%) †	7,191 (4.5)	101 (18.6)	0.976
Hypertension (%)	30,170 (18.9)	226 (41.7)	<0.001

Data are presented with mean (standard deviation), median (interquartile range), or percentage.

[a] ≥ 1 time per week, †Based on fasting blood glucose, history and medication use

BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

[b] ≥ college graduate

Table 2. Risks for all-cause mortality according to presence or absence of metabolic syndrome at baseline

Metabolic syndrome	Number of subjects	Person-years	Number of events	Incidence Density (10000 person-year)	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)
In all subjects						
Total	155,971					
MetS –	139,868	523,095.0	408	7.8	1.00 (reference)	1.00 (reference)
MetS +	20,103	74,533.3	134	18.0	1.19 (0.98-1.46)	1.15 (0.94-1.42)
Men	88,809					
MetS –	74,237	277,023.8	315	11.1	1.00 (reference)	1.00 (reference)
MetS +	14,572	71,095.4	99	14.9	1.08 (0.86-1.36)	1.06 (0.84-1.35)
Women	71,162					
MetS –	65,631	226,504.9	93	4.0	1.00 (reference)	1.00 (reference)
MetS +	5,531	23,004.1	35	16.5	1.89 (1.24-2.89)	1.82 (1.15-2.88)
After excluding subjects with DM, HTN						
Total	125,819					
MetS –	118,534	430,562.4	258	5.9	1.00 (reference)	1.00 (reference)
MetS +	7,285	35,966.6	22	7.2	0.92 (0.60-1.43)	0.89 (0.57-1.40)
Men	65,422					
MetS –	60,035	236,422.0	194	8.2	1.00 (reference)	1.00 (reference)
MetS +	5,387	19,488.0	15	7.7	0.78 (0.46-1.31)	0.77 (0.46-1.31)
Women	60,397					
MetS –	58,499	204,612.1	64	3.1	1.00 (reference)	1.00 (reference)
MetS +	1,898	6,006.9	7	11.7	1.88 (0.84-4.25)	1.80 (0.75-4.33)

[a] Adjusted for age, sex, smoking status, alcohol intake, regular exercise

HR, hazard ratio; CI, confidence interval; MetS, metabolic syndrome; DM, diabetes mellitus; HTN, hypertension

Table 3. Risks for all-cause mortality according to the number of metabolic syndrome components at baseline

Number of MetS components	Number of subjects	Person-years	Number of events	Incidence Density (10000 person-year)	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)
In all subjects						
Total	159,971					
0	66,355	244,697.9	131	5.4	1.00 (reference)	1.00 (reference)
1	45,682	172,987.6	142	8.2	0.93 (0.73-1.19)	0.93 (0.73-1.19)
2	27,931	105,409.4	135	12.8	1.04 (0.81-1.34)	1.03 (0.80-1.33)
3	14,258	53,418.2	95	17.8	1.22 (0.92-1.60)	1.18 (0.89-1.57)
4	5,127	18,685.3	34	18.2	1.10 (0.75-1.61)	1.04 (0.70-1.56)
5	718	2,429.8	5	20.6	1.16 (0.47-2.85)	0.93 (0.34-2.52)
P for trend					0.144	0.308
Men	88,809					
0	27,503	108,024.6	92	8.5	1.00 (reference)	1.00 (reference)
1	27,077	107,572.4	112	10.4	0.91 (0.69-1.20)	0.90 (0.68-1.20)
2	19,657	7,6847.8	111	14.4	1.02 (0.77-1.35)	1.00 (0.75-1.33)
3	10,457	40,412.2	68	16.8	1.03 (0.75-1.42)	1.01 (0.73-1.40)
4	3,712	13,901.8	26	18.7	1.02 (0.66-1.59)	1.01 (0.64-1.58)
5	403	1,360.4	5	36.8	1.75 (0.71-4.32)	1.38 (0.50-3.77)
P for trend					0.458	0.618
Women	71,162					
0	38,852	136,673.3	39	2.9	1.00 (reference)	1.00 (reference)
1	18,605	65,415.2	30	4.6	1.08 (0.66-1.75)	1.15 (0.69-1.91)
2	8,174	28,561.7	24	8.4	1.30 (0.75-2.25)	1.38 (0.77-2.45)
3	3,801	13,005.9	27	20.8	2.51 (1.44-4.37)	2.60 (1.45-4.69)
4	1,415	4,783.5	8	16.7	1.71 (0.76-3.87)	1.53 (0.61-3.83)
5	315	1,069.5	0	0	-	-
P for trend					0.022	0.038
After excluding subjects with DM, HTN						
Total	125,819					
0	64,821	240,065.4	124	5.2	1.00 (reference)	1.00 (reference)
1	36,769	138,172.6	80	5.8	0.79 (0.60-1.05)	0.80 (0.60-1.07)
2	16,944	62,796.1	54	8.6	0.94 (0.68-1.30)	0.92 (0.66-1.29)
3	5,925	20,948.4	18	8.6	0.85 (0.52-1.40)	0.82 (0.49-1.36)
4	1,256	4,237.7	4	9.4	0.84 (0.31-2.28)	0.84 (0.31-2.29)
5	104	308.8	0	0	-	-

P for trend					0.416	0.353
Men	65,422					
0	26,698	105,743.0	86	8.1	1.00 (reference)	1.00 (reference)
1	21,354	84,701.1	63	7.4	0.80 (0.58-1.10)	0.79 (0.57-1.11)
2	11,983	45,977.9	45	9.8	0.94 (0.66-1.36)	0.91 (0.62-1.31)
3	4,377	16,027.6	12	7.5	0.70 (0.38-1.28)	0.69 (0.37-1.26)
4	943	3,268.8	3	9.2	0.78 (0.25-2.48)	0.76 (0.24-2.42)
5	67	191.6	0	0	-	-
P for trend					0.296	0.234
Women	60,397					
0	38,123	134,322.4	38	2.8	1.00 (reference)	1.00 (reference)
1	15,415	53,471.5	17	3.2	0.86 (0.48-1.53)	0.92 (0.50-1.68)
2	4,961	16,818.2	9	5.4	1.07 (0.50-2.29)	1.24 (0.58-2.67)
3	1,548	4,920.8	6	12.2	1.97 (0.80-4.88)	1.93 (0.72-5.17)
4	313	968.9	1	10.3	1.39 (0.18-10.41)	1.70 (0.23-12.84)
5	37	117.2	0	0	-	-
P for trend					0.388	0.296

[a] Adjusted for age, sex, smoking status, alcohol intake, regular exercise

MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval; MetS, metabolic syndrome; DM, diabetes mellitus; HTN, hypertension;

Table 4. Risks for cardiovascular mortality according to presence or absence of metabolic syndrome at baseline

Metabolic syndrome	Number of subjects	Person-years	Number of events	Incidence Density (10000 person-year)	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)
In all subjects						
Total	155,971					
MetS -	139,868	523,095.0	69	1.3	1.00 (reference)	1.00 (reference)
MetS +	20,103	74,533.3	31	4.2	1.63 (1.06-2.52)	1.60 (1.02-2.20)
Men	88,809					
MetS -	74,237	292,444.8	52	1.8	1.00 (reference)	1.00 (reference)
MetS +	14,572	55,674.3	26	4.7	1.73 (1.07-2.78)	1.67 (1.02-2.72)
Women	71,162					
MetS -	65,631	230,650.2	17	0.7	1.00 (reference)	1.00 (reference)
MetS +	5,531	18,858.9	5	2.7	1.32 (0.45-3.84)	1.38 (0.42-4.57)
After excluding subjects with DM, HTN						
Total	125,819					
MetS -	118,534	441,034.1	34	0.8	1.00 (reference)	1.00 (reference)
MetS +	7,285	25,494.9	3	1.2	0.99 (0.30-3.25)	0.95 (0.29-3.12)
Men	65,422					
MetS -	60,035	23,6422.0	25	1.1	1.00 (reference)	1.00 (reference)
MetS +	5,387	19,488.0	3	1.5	1.22 (0.37-4.04)	1.14 (0.34-3.78)
Women	60,397					
MetS -	58,499	204,612.1	9	0.4	1.00 (reference)	1.00 (reference)
MetS +	1,898	6,006.9	0	0	-	-

[a] Adjusted for age, sex, smoking status, alcohol intake, regular exercise

HR, hazard ratio; CI, confidence interval; MetS, metabolic syndrome; DM, diabetes mellitus; HTN, hypertension;

Table 5. Risks for cardiovascular mortality according to the number of metabolic syndrome components at baseline

Number of MetS components	Number of subjects	Person-years	Number of events	Incidence Density (10000 person-year)	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)
In all subjects						
Total	159,971					
0	66,355	244,697.9	12	0.5	1.00 (reference)	1.00 (reference)
1	45,682	172,987.6	29	1.7	2.14 (1.08-4.22)	1.99 (1.00-3.95)
2	27,931	105,409.4	28	2.7	2.47 (1.23-4.93)	2.28 (1.13-4.60)
3	14,258	53,418.2	22	4.1	3.24 (1.57-6.68)	2.88 (1.37-6.03)
4	5,127	18,685.3	8	4.3	2.98 (1.19-7.46)	2.98 (1.19-7.46)
5	718	2,429.8	1	4.1	2.73 (0.35-21.25)	2.65 (0.34-20.70)
P for trend					0.002	0.004
Men	88,809					
0	27,503	108,024.6	8	0.7	1.00 (reference)	1.00 (reference)
1	27,077	107,572.4	19	1.8	1.82 (0.80-4.18)	1.71 (0.74-3.95)
2	19,657	76,847.8	25	3.3	2.74 (1.22-6.13)	2.59 (1.15-5.82)
3	10,457	40,412.2	18	4.5	3.29 (1.41-7.65)	2.96 (1.26-6.98)
4	3,712	13,901.8	7	5.0	3.31 (1.18-9.25)	3.22 (1.15-9.04)
5	403	1,360.4	1	7.4	4.22 (0.52-34.09)	4.02 (0.50-32.54)
P for trend					0.001	0.003
Women	71,162					
0	38,852	136,673.3	4	0.3	1.00 (reference)	1.00 (reference)
1	18,605	65,415.2	10	1.5	3.34 (1.01-11.01)	3.32 (0.99-11.14)
2	8,174	28,561.7	3	1.1	1.45 (0.30-7.03)	1.11 (0.19-6.59)
3	3,801	13,005.9	4	3.1	3.26 (0.72-14.86)	2.94 (0.57-15.23)
4	1,415	4,783.5	1	2.1	1.86 (0.19-18.44)	2.34 (0.23-23.78)
5	315	1,069.5	0	0	-	-
P for trend					0.550	0.548
After excluding subjects with DM, HTN						
Total	125,819					
0	64,821	240,065.4	12	0.5	1.00 (reference)	1.00 (reference)
1	36,769	138,172.6	13	0.9	1.39 (0.63-3.07)	1.37 (0.62-3.03)
2	16,944	62,796.1	9	1.4	1.74 (0.72-4.20)	1.69 (0.70-4.08)
3	5,925	20,948.4	2	1.0	1.06 (0.23-4.80)	1.02 (0.22-4.61)
4	1,256	4,237.7	1	2.4	2.42 (0.31-18.83)	2.24 (0.29-17.52)
5	104	308.8	0	0	-	-

P for trend					0.325	0.381
Men	65,422					
0	26,698	105,743.0	8	0.8	1.00 (reference)	1.00 (reference)
1	21,354	84,701.1	9	1.1	1.25 (0.48-3.24)	1.21 (0.47-3.15)
2	11,983	45,977.9	8	1.7	1.88 (0.70-5.02)	1.77 (0.66-4.75)
3	4,377	16,027.6	2	1.2	1.28 (0.27-6.07)	1.19 (0.25-5.63)
4	943	3,268.8	1	3.1	2.94 (0.37-23.62)	2.56 (0.32-20.71)
5	67	191.6	0	0	-	-
P for trend					0.236	0.311
Women	60,397					
0	38,123	134,322.4	4	0.3	1.00 (reference)	1.00 (reference)
1	15,415	53,471.5	4	0.7	2.00 (0.48-8.26)	2.10 (0.51-8.64)
2	4,961	16,818.2	1	0.6	1.23 (0.13-11.91)	1.29 (0.13-12.44)
3	1,548	4,920.8	0	0	-	-
4	313	968.9	0	0	-	-
5	37	117.2	0	0	-	-
P for trend					0.992	0.942

[a] Adjusted for age, sex, smoking status, alcohol intake, regular exercise

HR, hazard ratio; CI, confidence interval; MetS, metabolic syndrome; DM, diabetes mellitus; HTN, hypertension;

Table 6. Risks for all-cause mortality according to metabolic syndrome components at baseline

Components of metabolic syndrome	In all subjects		After excluding subjects with DM		After excluding subjects with DM, HTN	
	full-adjusted HR (95% CI)	Stepwise HR[a] (95% CI)	full-adjusted HR (95% CI)	Stepwise HR[a] (95% CI)	full-adjusted HR (95% CI)	Stepwise HR[a] (95% CI)
Total	N=155,971		N=152,679		N=125,819	
Fasting blood glucose	1.40 (1.16-1.69)	1.41 (1.17-1.70)	1.13 (0.91-1.42)	-	1.07 (0.80-1.45)	-
Blood pressure	1.27 (1.05-1.53)	1.28 (1.06-1.54)	1.29 (1.04-1.59)	1.30 (1.05-1.60)	1.34 (0.97-1.86)	-
Triglyceride	0.65 (0.53-0.79)	0.65 (0.54-0.79)	0.67 (0.53-0.83)	0.67 (0.54-0.83)	0.65 (0.48-0.87)	-
High-density lipoprotein cholesterol	1.06 (0.81-1.37)	-	0.94 (0.69-1.29)	-	1.14 (0.78-1.65)	-
Waist circumference	1.05 (0.85-1.28)	-	1.06 (0.84-1.33)	-	0.91 (0.65-1.26)	-
Men	N=87,261		N=82,342		N=64,358	
Fasting blood glucose	1.32 (1.07-1.63)	1.32 (1.07-1.63)	1.05 (0.82-1.35)		0.96 (0.69-1.35)	
Blood pressure	1.24 (1.01-1.53)	1.24 (1.01-1.53)	1.19 (0.94-1.51)	-	1.29 (0.89-1.85)	-
Triglyceride	0.68 (0.55-0.84)	0.68(0.55-0.84)	0.68 (0.54-0.87)	-	0.67 (0.49-0.92)	-
High-density lipoprotein cholesterol	1.04 (0.74-1.45)	-	0.93 (0.62-1.39)	-	1.28 (0.81-2.03)	-
Waist circumference	1.02 (0.81-1.28)	-	1.05 (0.81-1.36)	-	0.86 (0.60-1.24)	-
Women	N=67,299		N=65,266		N=57,488	
Fasting blood glucose	1.77 (1.17-2.68)	1.85 (1.24-2.77)	1.51 (0.94-2.39)		1.62 (0.87-3.01)	
Blood pressure	1.46 (0.95-2.23)	-	1.83 (1.16-2.88)	1.81 (1.15-2.83)	1.67 (0.80-3.48)	-
Triglyceride	0.59 (0.36-0.97)	-	0.68 (0.39-1.16)	-	0.67 (0.31-1.45)	-
High-density lipoprotein cholesterol	1.13 (0.73-1.74)	-	1.02 (0.63-1.66)	-	1.00 (0.53-1.86)	-
Waist circumference	1.28 (0.80-2.04)	-	1.20 (0.71-2.03)	-	1.27 (0.60-2.71)	-

[a] Adjusted for age, sex, smoking status, alcohol intake, regular exercise

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease

Table 7. Risks for cardiovascular mortality according to metabolic syndrome components at baseline

	In all subjects		After excluding subjects with DM		After excluding subjects with DM, HTN	
Components of metabolic syndrome	**full-adjusted HR (95% CI)**	**Stepwise HR[a] (95% CI)**	**full-adjusted HR (95% CI)**	**Stepwise HR[a] (95% CI)**	**full-adjusted HR (95% CI)**	**Stepwise HR[a] (95% CI)**
Total	N=155,971		N=152,679		N=125,819	
Fasting blood glucose	0.94 (0.61-1.47)		0.76 (0.45-1.30)		0.85 (0.37-1.98)	
Blood pressure	2.87 (1.83-4.50)	2.90 (1.86-4.52)	3.17 (1.95-5.15)	3.20 (1.98-5.16)	1.92 (0.85-4.30)	-
Triglyceride	0.90 (0.58-1.38)	-	0.87 (0.54-1.40)	-	0.93 (0.45-1.94)	-
High-density lipoprotein cholesterol	1.16 (0.64-2.10)	-	1.23 (0.65-2.34)	-	2.13 (0.93-4.85)	-
Waist circumference	1.21 (0.77-1.89)	-	1.21 (0.73-1.99)	-	0.79 (0.32-1.93)	-
Men	N=87,261		N=82,342		N=64,358	
Fasting blood glucose	0.92 (0.57-1.50)		0.75 (0.42-1.36)		0.87 (0.34-2.18)	
Blood pressure	2.59 (1.57-4.27)	2.73 (1.67-4.48)	2.76 (1.61-4.74)	2.88 (1.69-4.91)	1.61 (0.64-4.05)	-
Triglyceride	1.06 (0.66-1.70)	-	0.99 (0.59-1.68)	-	1.17 (0.53-2.58)	-
High-density lipoprotein cholesterol	0.98 (0.47-2.08)	-	1.10 (0.49-2.46)	-	2.01 (0.74-5.48)	-
Waist circumference	1.47 (0.91-2.37)	-	1.42 (0.83-2.44)	-	0.93 (0.37-2.34)	-
Women	N=67,299		N=65,266		N=57,488	
Fasting blood glucose	1.08 (0.37-3.18)	1.24 (0.43-3.56)	0.83 (0.23-3.04)		0.81 (0.10-6.78)	
Blood pressure	4.58 (1.62-12.92)	7.19 (2.81-18.42)	5.97 (1.99-17.87)	8.50 (3.17-22.75)	3.78 (0.72-19.78)	5.24 (1.08-25.52)
Triglyceride	0.30 (0.07-1.36)	-	0.39 (0.08-1.81)	-	-	-
High-density lipoprotein cholesterol	1.92 (0.71-5.17)	-	1.82 (0.62-5.30)	-	2.91 (0.71-11.84)	-
Waist circumference	0.39 (0.08-1.79)	-	0.55 (0.12-2.61)	-	-	-

[a] Adjusted for age, sex, smoking status, alcohol intake, regular exercise

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease