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ORIGINAL ARTICLE
Metabolic Disorder

Impact of Metabolic Syndrome Independent of Insulin Resistance on the Development of Cardiovascular Disease

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Background: It is controversial as to whether metabolic syndrome is a predictor of cardiovascular disease (CVD) independent of insulin resistance (IR). The aim of this study was to determine the independent and combined effects of metabolic syndrome and IR on the incidence of CVD in a prospective cohort study.

Methods and Results: A total of 6,430 healthy subjects who underwent a health check-up were enrolled. Risk factors for atherosclerotic CVD (ASCVD) including ischemic heart disease (IHD) and stroke were measured. The prevalence of metabolic syndrome and IR were 24.4% and 25.6%, respectively. There were 644 incident cases (9.0%) of ASCVD diagnosed in the cohort. After adjusting for traditional confounders and IR, metabolic syndrome was related to the incidence of CVD. In the multivariate model, the hazard ratios (95% confidence intervals) of metabolic syndrome for IHD, stoke, and ASCVD were 1.66 (1.32–2.09), 1.60 (1.21–2.12), and 1.61 (1.36–1.90), respectively. The risk of IHD, stoke, and ASCVD increased with increasing number of metabolic syndrome components. Furthermore, the risk of CVD was stronger in those who had both metabolic syndrome and IR concurrently.

Conclusions: Metabolic syndrome is related to the incidence of CVD independent of IR. Also, the combined effect of metabolic syndrome and IR contributes to the risk of CVD. (*Circ J* 2012; **76:** 2443–2448)

Key Words: Cardiovascular disease; Insulin resistance; Ischemic heart disease; Metabolic syndrome; Stroke

Metabolic syndrome is a cluster of metabolic abnormalities, central to which are obesity, hyperglycemia, hypertriglyceridemia, decreased high-density lipoprotein cholesterol (HDL-C), and elevated blood pressure. Metabolic syndrome has been shown to increase the risk of cardiovascular disease (CVD), and the prevalence of metabolic syndrome is rapidly increasing. The prevalence of metabolic syndrome among adults aged ≥20 years was 27.3% using the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATP III) in the National Health and Nutrition Examination Survey (NHANES; 1988–1994).[1] Using the modified NCEP-ATP III from WHO WPRO, the prevalence of metabolic syndrome was 23.6% in an analysis of the Korean National Health and Nutrition Examination Survey (KNHANES) data from 1998 and significantly increased to 28.0% in 2001.[2] It showed that the prevalence of metabolic syndrome increased by 4.4% during 3 years.

Metabolic syndrome is also known as insulin resistance (IR) syndrome based upon IR, and increases the risk of developing CVD and increases the prevalence or mortality of type 2 diabetes.[3,4] Recent studies have reported that metabolic syndrome and IR are risk factors of CVD.[5–9] The importance of metabolic syndrome in these studies was highlighted because it increased the risk of CVD based on IR being present.[10] IR is hypothesized to be the central feature of metabolic syndrome,[11] but it is unclear if metabolic syndrome predicts CVD independent of IR.

Most studies in regard to the association between metabolic syndrome and CVD risk factors for the Korean population are cross-sectional.[12–14] In Korea, no studies have been attempted on the association between metabolic syndrome and CVD in prospective studies. The objective of this study was to determine the independent and combined effects of metabolic syndrome and IR for the incidence of CVD in a prospective cohort study.

Methods

Subjects

This study was a subcohort of Seoul Metabolic Syndrome Initiatives (SMSRI), which started in 2005. The number of participants who underwent medical examination offered by

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Table 1. Subject Baseline Characteristics (n=6,430)

	Men (n=3,726)	Women (n=2,704)
	Mean±SD	Mean±SD
Age (years)	48.9±9.3	48.8±9.2
Body mass index (kg/m^2)	23.8±2.6	23.0±2.9
SBP (mmHg)	123.6±15.5	122.1±16.6
DBP (mmHg)	83.9±10.8	79.2±11.5
Total cholesterol (mg/dl)	198.2±34.3	193.8±35.6
Triglycerides (mg/dl)	160.6±93.6	111.2±72.2
Log triglycerides	2.1±0.2	2.0±0.2
HDL-C (mg/dl)	47.5±11.4	55.6±12.9
Fasting plasma glucose (mg/dl)	105.6±28.7	94.8±20.8
Insulin	7.6±4.0	7.1±3.8
HOMA	2.0±1.2	1.7±1.2
	%	%
Smoking status		
Ex smoker	30.6	9.3
Current smoker	50.3	5.4
Regular exercise		
Yes	27.8	46.3
IR (HOMA-IR)		
Yes	28.8	19.8
MetS		
Yes	28.7	18.5

DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; MetS, metabolic syndrome; SBP, systolic blood pressure.

Samsung Medical Center in 1997 was 42,791. Among the total sample, 7,196 participants aged ≥30 years with an insulin measurement were included. Among the 7,196, we excluded participants with any missing data for height, weight, blood pressure, triglyceride, cholesterol (total cholesterol, HDL-C), and fasting glucose. Participants were excluded if they had atherosclerotic CVD (ASCVD) and any cancer at baseline. In addition, subjects with an extremely low body mass index (BMI; <16 kg/m^2 or >40 kg/m^2) were excluded. Therefore, the final subject group consisted of 6,430 Korean men and women (men, n=3,726; women, n=2,704). The mean follow-up period was 10 years. The study was approved by Institutional Review Boards of the Yonsei University College of Medicine and the Samsung Medical Center.

Data Collection

Each participant was interviewed using a structured questionnaire to collect the following details: smoking history (never smoked, ex-smoker, or current smoker), alcohol consumption (non-drinker or consumers of any amount of alcohol on a regular basis), regular exercise (yes or no), hypertension, diabetes and medication taken for hypertension and diabetes. Participant height and weight was measured while wearing light clothing. BMI was calculated by dividing weight (kg) by height squared (m^2). Systolic and diastolic blood pressures were measured after a 15-min rest period.

Biomarker Measurement

For clinical chemistry assays, serum samples were obtained from peripheral venous blood samples obtained after 12 h of fasting, and then stored at –70°C. Biomarkers for metabolic syndrome, namely fasting blood glucose, total cholesterol, triglyceride, and HDL-C, were measured using a COBAS INTEGRA 800 and a Hitachi-7600 analyzer (Hitachi, Tokyo). The homeostatic model assessment-insulin resistance (HOMA-IR) was calculated from fasting serum insulin levels as follows: fasting serum insulin (μUnits/ml)×fasting plasma glucose (mmol/L)/22.5.[15]

Definition of Metabolic Syndrome and IR

Metabolic syndrome was defined as the presence of at least 3 of the 5 characteristics of metabolic syndrome described by the ATP-III of the Korean National Cholesterol Education Program.[16] The cut-offs for the definition of obesity in Asian populations have been revised,[17] the criteria for metabolic syndrome was modified using the definition of BMI.

The following criteria were used to define metabolic syndrome: (1) obesity (BMI ≥25 kg/m^2); (2) high triglyceride (≥150 mg/dl); (3) low HDL-C (<40 mg/dl for men and <50 mg/dl for women); (4) high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) and (5) hyperglycemia (fasting plasma glucose ≥110 mg/dl).

As one of the indirect indexes for diagnosing IR, a previous study used fasting plasma insulin, considering the 75th percentile in the target population to be the IR index.[18] Subjects with HOMA-IR ≥2.27 were defined as the highest quartile for IR.

Incidence of CVD

The incidence of CVD between 1997 and 2007 was estimated using National Health Insurance Corporation hospitalization bills. Among the bills, the earliest was assumed as the baseline of disease incidence. International Classification of Disease, Tenth Revision (ICD-10) codes for insurance reimbursement were used as a surrogate marker of incidence of CVD. The first factor for ASCVD consisted of hypertensive disease (ICD-10 codes I10–I15), ischemic heart disease (IHD, I20–I25), hemorrhagic stroke (I60–I62), thrombotic stroke (I63), other stroke (I64–I69), other heart disease likely related to ASCVD (I44–I51) and other vascular disease (I70–I74). For those individuals with more than 1 event, we used only the first event in our analysis.

We performed IHD event validation, in collaboration with the Korean Heart Association by forming the Event Validation Committee (EVC), from July 2008 to May 2009.[19] In subjects who gave written permission for using personal information for the study, 673 CHD events were confirmed by individual hospital medical checks. The accuracy of acute myocardial infarction diagnosis using ICD-10 codes in Korean medical claims data was >70% and reliability was good to fair.

Statistical Analysis

We calculated hazard ratios (HRs) using Cox proportional hazards modeling to adjust for age and other potential confounding factors such as age, sex, smoking status, alcohol drinking, and exercise. A Cox proportional hazards model was used to model time to event for estimation of relative risks of cardiovascular incidence. Initially, we fitted independent models of metabolic syndrome and IR for CVD. In the secondary analyses, we fitted an additional model with the combined effect of metabolic syndrome and IR for CVD. Reference categories were no metabolic syndrome and no IR. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC, USA). All statistical tests were 2-sided, and statistical significance was accepted for P<0.05.

Table 2. Baseline Subject Characteristics vs. Presence of MetS and IR

	No MetS			MetS		
	No IR	IR	P value	No IR	IR	P value
Men						
n	2,154	504		498	570	
Age (years)	48.3±9.0	49.1±9.7	0.0835	50.1±9.4	50.0±9.6	0.7872
Body mass index (kg/m^2)	22.8±2.3	24.3±2.3	<0.0001	25.1±2.1	26.1±2.4	<0.0001
SBP (mmHg)	120.1±14.7	123.6±15.0	<0.0001	129.0±15.0	132.0±14.9	0.0009
DBP (mmHg)	81.5±10.3	83.6±10.6	<0.0001	88.1±10.2	89.2±9.8	0.0689
Total cholesterol (mg/dl)	194.0±32.4	198.6±33.7	0.0050	201.5±34.7	210.9±37.3	<0.0001
Triglycerides (mg/dl)	129.4±64.3	151.6±76.9	<0.0001	210.5±84.3	242.6±132.5	<0.0001
HDL-C (mg/dl)	50.4±11.4	48.4±9.7	<0.0001	40.7±9.3	41.6±9.6	0.1237
Fasting blood glucose (mg/dl)	98.2±17.6	114.5±39.3	<0.0001	104.8±22.1	126.1±41.8	<0.0001
Insulin	5.6±2.0	11.8±4.0	<0.0001	6.5±1.7	12.3±4.3	<0.0001
HOMA	1.3±0.5	3.2±1.2	<0.0001	1.6±0.4	3.6±1.4	<0.0001
Women						
n	1,894	310		276	224	
Age (years)	47.3±8.8	48.8±9.6	0.0103	55.0±8.3	53.3±8.3	0.0217
Body mass index (kg/m^2)	22.2±2.5	23.9±2.7	<0.0001	25.1±2.5	26.3±2.8	<0.0001
SBP (mmHg)	118.5±14.9	122.3±14.6	<0.0001	135.9±16.6	135.6±17.7	0.8367
DBP (mmHg)	76.6±10.4	79.3±9.9	<0.0001	88.9±11.0	88.7±11.6	0.7930
Total cholesterol (mg/dl)	189.7±34.8	200.0±35.4	<0.0001	204.1±36.1	206.4±35.9	0.4830
Triglycerides (mg/dl)	90.8±42.3	114.7±64.6	<0.0001	170.9±85.7	205.5±127.2	0.0006
HDL-C (mg/dl)	58.8±12.5	53.3±10.7	<0.0001	44.7±8.8	44.9±9.5	0.8545
Fasting blood glucose (mg/dl)	89.6±9.1	102.9±23.4	<0.0001	96.8±21.2	124.6±45.1	<0.0001
Insulin	5.7±2.1	12.6±3.8	<0.0001	6.3±2.0	13.0±4.7	<0.0001
HOMA	1.2±0.5	3.1±1.0	<0.0001	1.5±0.5	3.9±2.2	<0.0001

Data given as mean±SD. Abbreviations as in Table 1.

Table 3. Association Between MetS and CVD

	Men (n=3,726)			Women (n=2,704)		
	n	MetS–	MetS+	n	MetS–	MetS+
		HR	HR (95% CI)		HR	HR (95% CI)
Model 1						
IHD	197	1.0	1.96 (1.48–2.60)	77	1.0	1.89 (1.17–3.05)
Total stroke	106	1.0	1.48 (1.00–2.20)	82	1.0	2.64 (1.69–4.12)
ASCVD	330	1.0	1.69 (1.36–2.11)	185	1.0	2.19 (1.62–2.96)
Model 2						
IHD	197	1.0	1.65 (1.22–2.23)	77	1.0	1.98 (1.20–3.26)
Total stroke	106	1.0	1.30 (0.86–1.97)	82	1.0	2.37 (1.49–3.75)
ASCVD	330	1.0	1.44 (1.14–1.82)	185	1.0	2.07 (1.51–2.83)
Model 3						
IHD	197	1.0	1.67 (1.24–2.24)	77	1.0	1.93 (1.17–3.19)
Total stroke	106	1.0	1.30 (0.86–1.97)	82	1.0	2.56 (1.62–4.05)
ASCVD	330	1.0	1.46 (1.16–1.84)	185	1.0	2.12 (1.55–2.89)

Model 1 adjusted for age, smoking status, alcohol drinking, and exercise; model 2 adjusted for age, smoking status, alcohol drinking, exercise, and insulin resistance (yes/no); model 3 adjusted for age, smoking status, alcohol drinking, exercise, and HOMA-IR (continuous).
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio. Other abbreviations as in Table 1.

Results

General baseline subject characteristics are listed in Table 1. The mean age for both genders was approximately 49 years. The average BMI was 23.8 kg/m^2 for men and 23.0 kg/m^2 for women. The mean systolic blood pressure, diastolic blood pressure and fasting blood sugar were also similar in both genders, but higher triglyceride was seen in men. There was a significantly higher rate of smoking and alcohol consumption in men than women. According to the NCEP definitions, the prevalence of metabolic syndrome at baseline was 28.7% in men and 18.5% in women. The baseline prevalence of IR was 28.8% in men and 19.8% in women.

Table 2 lists the subject baseline characteristics according

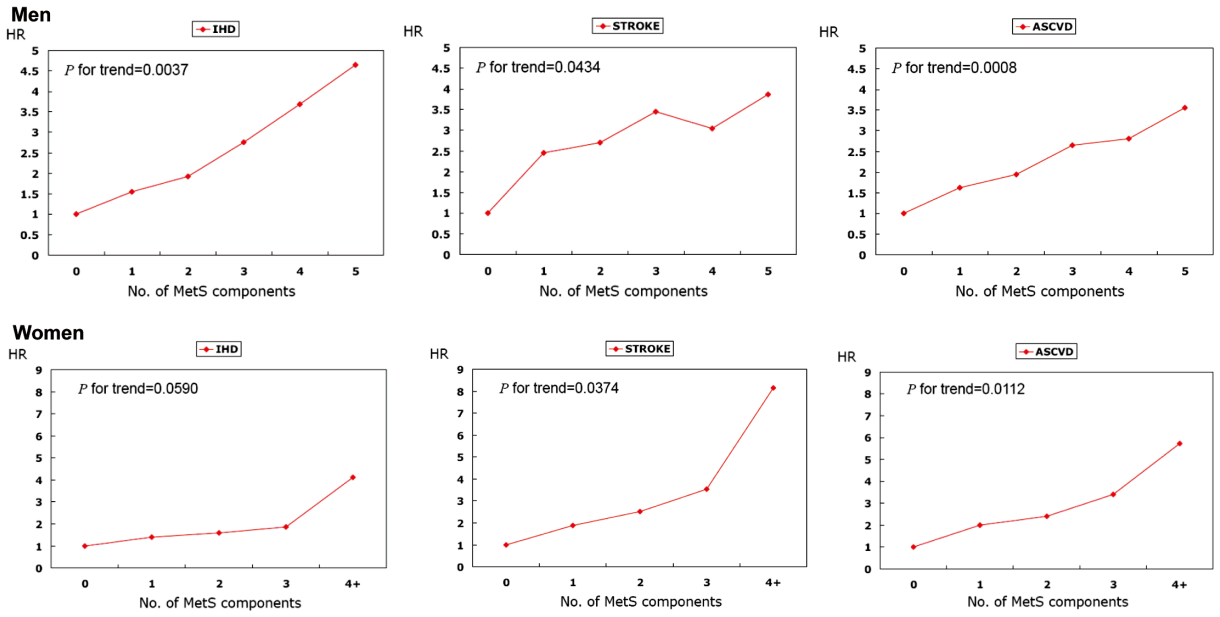

Figure. Hazard ratios (HRs) for ischemic heart disease (IHD), stroke, and atherosclerotic cardiovascular disease (ASCVD) according to number of metabolic syndrome (MetS) components.

Table 4. Combined Effects of MetS and IR for CVD

	Total	IHD		Total stroke		ASCVD	
		n	HR† (95% CI)	n	HR† (95% CI)	n	HR† (95% CI)
Men							
MetS–, IR–	2,154	77	1.0	46	1.0	137	1.0
MetS+, IR–	498	31	1.52 (1.00–2.31)	17	1.41 (0.81–2.46)	51	1.40 (1.01–1.94)
MetS–, IR+	504	29	1.54 (1.01–2.37)	18	1.60 (0.93–2.76)	53	1.60 (1.17–2.20)
MetS+, IR+	570	60	2.79 (1.98–3.91)	25	1.89 (1.16–3.09)	89	2.36 (1.81–3.09)
Women							
MetS–, IR–	1,894	41	1.0	30	1.0	85	1.0
MetS+, IR–	276	19	2.08 (1.18–3.68)	22	2.83 (1.61–4.99)	44	2.19 (1.50–3.19)
MetS–, IR+	310	7	0.92 (0.41–2.06)	12	2.02 (1.03–3.97)	22	1.37 (0.85–2.19)
MetS+, IR+	224	10	1.57 (0.78–3.16)	18	3.50 (1.94–6.33)	34	2.52 (1.68–3.77)

†Adjusted for age, smoking, alcohol drinking, and exercise. Abbreviations as in Tables 1,3.

to metabolic syndrome and IR. The prevalence of metabolic syndrome with IR was 15.3% in men and 8.3% in women. In subjects without metabolic syndrome at baseline, there were statistically significant differences between the subjects with and without IR in all parameters. In subjects with metabolic syndrome, there were significant differences between the subjects with and without IR in terms of BMI, systolic blood pressure, total cholesterol, triglyceride, fasting glucose, insulin, and HOMA. Systolic blood pressure and total cholesterol were significantly different in men, but not in women.

Table 3 lists the association between metabolic syndrome and CVD after adjusting for age, sex, smoking status, alcohol intake, and exercise, which were determined in both men and women. In men, the HR (95% confidence interval [CI]) of metabolic syndrome for IHD, stoke, and ASCVD was 1.96 (1.48–2.60), 1.48 (1.00–2.20), and 1.69 (1.36–2.11), respectively. In women, the HR (95%CI) of metabolic syndrome for IHD, stoke, and ASCVD was 1.89 (1.17–3.05), 2.64 (1.69–4.12), and 2.19 (1.62–2.96), respectively. In addition, after further adjustment for IR (or HOMA-IR), the risk of IHD, stroke, and ASCVD slightly attenuated with metabolic syndrome, but it remained significant. The presence of metabolic syndrome was not seen to be significant HR against total stroke in men in models 2 and 3 after adjustment for HOMA-IR. After further adjustment for low-density lipoprotein cholesterol, metabolic syndrome was related to the incidence of CVD, but the statistical significance of the results did not change (data not shown). Metabolic syndrome was found to be associated with CVD independent of IR.

We also explored whether increasing the number of metabolic syndrome components might affect the development of CVD by measuring HRs in both men and women after adjusting for age, smoking, alcohol drinking and exercise. We found a trend for the HR for IHD, total stroke and ASCVD to in-

crease with increasing number of metabolic syndrome components. Women with even 1 component of metabolic syndrome had a significantly higher HR for CVD relative to subjects without any components of metabolic syndrome; among individuals with ≥4 components present, the HRs for incident IHD, stroke, ASCVD were 3.86 (95% CI: 2.09–7.14), 3.19 (95% CI: 1.22–8.34), and 2.94 (95% CI: 1.82–4.75) in men and 4.12 (95% CI: 1.80–9.41), 8.16 (95% CI: 3.19–20.86), and 5.73 (95% CI: 3.14–10.46) in women, compared with the respective subgroups with no components of the metabolic syndrome (**Figure**).

We examined the combined effects of metabolic syndrome and IR for CVD (**Table 4**). After adjusting for confounding variables, subjects with metabolic syndrome and IR were found to have a higher risk of CVD than those without metabolic syndrome and IR. Subjects with metabolic syndrome and IR compared to those with metabolic syndrome and without IR had a 2.36-fold (95% CI: 1.81–3.09) increase in men and a 2.52-fold increase (95% CI: 1.68–3.77) in women for the risk of ASCVD. The male subjects who had high HOMA-IR without metabolic syndrome were at risk of IHD. The risk of IHD in subjects with both metabolic syndrome and high HOMA-IR was not statistically significant in women.

Discussion

In a relatively large-scale prospective cohort study among the Korean population, this study found an association between metabolic syndrome, IR and CVD. Metabolic syndrome was associated with risk of CVD independent of IR for 10 years of follow-up. Also, the HR for CVD increased with increasing number of metabolic syndrome components. In addition, women with even 1 component of metabolic syndrome had a significantly higher HR for CVD relative to subjects without any components of metabolic syndrome. Furthermore, the risk of CVD was stronger in those who had both metabolic syndrome and IR concurrently.

Several studies have been published focusing on the independent associations of IR or metabolic syndrome with CVD. The risks of CVD associated with the various metabolic syndrome components in the present study were compatible with other population studies.[3,20–23] In the Taiwan community, metabolic syndrome was highly prevalent among the adult population and associated with an increased risk for coronary heart disease and stroke.[23] Previous cohort studies containing both diabetic and non-diabetic adults have found relationships between IR and CVD. In the San Antonio Heart Study, it showed that among non-diabetic individuals, the fourth and fifth quintiles of HOMA-IR were significant predictors of incident CVD during 8 years of follow-up.[24] Among a diabetic subject group, HOMA-IR was also an independent predictor of incident CVD.[25]

Metabolic syndrome is known to be closely related to IR, but the extent to which the metabolic syndrome and IR overlap has not been well delineated. It is controversial whether IR should be added to the list of metabolic syndrome components.[26–28] In the present study, metabolic syndrome was independently related to the incidence of CVD after adjusting for age, sex, smoking, alcohol drinking, exercise, and IR. The present results are consistent with previous studies. Several studies have concluded that both IR and metabolic syndrome simultaneously predict the presence of CVD.[29–32] In a Danish study, both HOMA-IR and metabolic syndrome were independent predictors of incident CVD.[33] In the Multi-Ethnic Study of Atherosclerosis (MESA) study, however, although HOMA-IR was associated with increased subclinical atherosclerosis, the association was not independent of the risk factors that comprise metabolic syndrome.[31] In the Framingham Offspring Study, metabolic syndrome and HOMA-IR did not independently predict the incidence of CVD. Resnick et al reported that the reason for inconsistent findings may be differences in the distribution of key risk factors between the cohorts, notably obesity, or to differences in the distribution of currently unknown genetic factors that may modify the effects of IR on heart disease in different ethnic groups.[8] For metabolic syndrome as high HOMA-IR, the HR of IHD in women was not significant whereas statistically significant HR of IHD was obtained in men. Moreover, in the present study, despite the lack of statistical significance of HR of IHD in women, the number of IHD cases was small and a positive association was observed. Therefore, it cannot be concluded that a gender difference may exist in the present findings. These findings and validity of the mechanism should be tested in further studies.

The potential limitations of the present study require some consideration. We had only HOMA-IR and did not directly measure IR. HOMA-IR, however, is also known to be closely related to the glucose clamp techniques ($r=-0.820$, $P<0.0001$).[34] It should also be kept in mind that the present study was conducted on apparently healthy people who voluntarily underwent a health checkup at hospital, which presents difficulties concerning the generalization of the present results. Evidence is continuing to mount linking this metabolic pattern not only to CVD but to other major chronic conditions. High insulin and IR are common features of industrialized societies characterized by a large prevalence of overweight and obesity, diet rich in energy intake, and a lifestyle characterized by low calorie expenditure.[35] The cost of measuring serum insulin in everybody, however, may be beyond routine health examination. It must be important to select the subjects with a possibility of high HOMA-IR. Nevertheless, this study is meaningful in that it is the first prospective cohort study of the individual and combined effects of IR and metabolic syndrome and their association with the risk of CVD in the Korean population. Also, the present study evaluated the association of metabolic syndrome with several endpoints such as IHD, stroke, and ASCVD.

In conclusion, in the present prospective cohort study, it was found that metabolic syndrome was associated with the risk of CVD independent of IR in Korean subjects. We showed that metabolic syndrome alone can be used as a predictor of CVD. Furthermore, we should monitor the healthy insulin-resistant population to prevent ongoing CVD.

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