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Risks for cardiovascular disease, stroke, ischaemic heart disease, and diabetes mellitus associated with the metabolic syndrome using the new harmonised definition: Findings from nationally representative longitudinal data from an Asian population

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ABSTRACT

Objective: We examined the risk of cardiovascular disease, stroke, ischaemic heart disease, and diabetes with the metabolic syndrome according to the new harmonised definition and its components using a national longitudinal data set from an Asian population.
Methods: Data of 9791 men and women aged 20+ from 1998 and 2001 Korea National Health and Nutrition Examination Surveys were individually linked to national hospitalisation and mortality data using unique personal identification numbers. During a 5.8-year follow-up through 2005, 288 incident cardiovascular events (184 strokes and 122 cases of ischaemic heart disease) and 85 new diabetes cases have been detected.
Results: Men and women with the metabolic syndrome had 48%, 39%, 64%, and 127% greater risks of cardiovascular disease, stroke, ischaemic heart disease, and diabetes, respectively, than those without the metabolic syndrome. The increased risks of cardiovascular disease, ischaemic heart disease, and diabetes remained significant after adjusting for health behaviours, bio-clinical factors, family history, and socio-demographic factors. Analysis results on population attributable risks showed that about a quarter of total diabetes occurrence and more than 10% of cardiovascular disease was attributable to the metabolic syndrome. The number of metabolic syndrome components was linearly associated with risks of outcomes. High blood pressure was significantly associated with all four outcomes while hypertriglyceridemia and hyperglycemia were also important for ischaemic heart disease and diabetes, respectively.
Conclusions: Reduction of metabolic risk factors is necessary in South Korea to lower the burden of associated diseases, especially ever-increasing ischaemic heart disease and diabetes.

1. Introduction

Since Reaven formalised the concept of "Syndrome X" [1], now known as "the metabolic syndrome", research efforts to explore the association between the metabolic syndrome and risk of cardiovascular disease and diabetes have been common in the West [2–4]. Recent meta-analyses of cohort studies have provided strong evidence that people with the metabolic syndrome are at increased risk of cardiovascular disease and diabetes [5–7]. Several community-based prospective studies have demonstrated the association of the metabolic syndrome with cardiovascular and diabetes events among Asian populations in Hong Kong [8,9], Japan [10–12], mainland China [13], Taiwan [14,15], and Thailand [16]. However, investigations into the relationship between the metabolic syndrome and future cardiovascular and diabetes risks remained underdeveloped in South Korea (hereafter "Korea"). Except for a few studies in Japan, the US and Turkey [12,17,18], the longitudinal relationship between the metabolic syndrome and health outcomes has not been demonstrated in a nationally representative sample. Asian studies have rarely presented the relationship of the metabolic syndrome with future risks of stroke, ischaemic heart disease, and diabetes simultaneously. The aim of our study was to examine the risk of cardiovascular disease, stroke, ischaemic heart disease, and diabetes with the metabolic syndrome and its components using a national longitudinal data set from an Asian population.

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2. Methods

2.1. Study subjects

We obtained data from the two waves of the Korea National Health and Nutrition Examination Survey (K-NHANES) conducted in November–December 1998 and 2001 by the Ministry of Health and Welfare of Korea and the Korea Institute for Health and Social Affairs. Information was collected from a stratified multistage probability sample of Korean households representing the civilian, non-institutionalised population. The response rates in K-NHANES were 86.5% in 1998 and 77.3% in 2001. A total of 14,563 men and women aged 20+ participated in the 1998 (7962 subjects) and 2001 (6601 subjects) K-NHANES health examination survey. Of these, 12,801 reported valid 13-digit personal identification numbers (PINs), which were linked to hospitalisation data from the Health Insurance Review and Assessment Service (HIRA) and mortality data from the National Statistical Office (NSO) of Korea.

We excluded the 107 pregnant women from the study. Using a checklist that included 37 potential illnesses in 1998 and 53 potential illnesses in 2001, we also identified and excluded participants who had any of the following during the previous year: stroke, ischaemic heart disease, diabetes, or cancer. We also excluded those receiving diabetes drug treatment and those with fasting serum glucose of 126 mg/dl or over. A total of 1411 subjects were excluded because they had any of the following: stroke, ischaemic heart disease, diabetes or cancer. Additionally, we excluded respondents with data lacking any clinical, behavioural, or socioeconomic variables ($n = 1492$). Hospitalisation and mortality follow-ups through December 2005 were made for the remaining 9791 men and women aged 20+ (5872 subjects from the 1998 and 3919 subjects from the 2001 K-NHANES) (see Supplementary Fig. 1).

The Institutional Review Board of the Asan Medical Center, Seoul, Korea, approved our study.

2.2. Outcome ascertainment

The outcome variables were morbidity or mortality events of cardiovascular disease, stroke, ischaemic heart disease, and diabetes. For those individuals with more than one event for each outcome during the follow-up period, we calculated survival times between baseline and the time of the first event. Using subjects' unique 13-digit PINs, both nonfatal and fatal outcomes were ascertained from HIRA hospital admission and discharge data and NSO mortality data. The HIRA data included all hospital admissions and discharges, as the National Health Insurance in Korea covers all Korean citizens. NSO adult death certificate data are known to be complete. Thus, the follow-up rate for outcomes would reach 100%. We used International Classification of Diseases, 10th Revision codes to identify stroke (I60–I69), ischaemic heart disease (I20–I25), and diabetes (E10–E14). In this study, stroke and ischaemic heart disease constituted cardiovascular disease. Morbidity and mortality follow-up started in January 1999 for the 1998 and in January 2002 for the 2001 K-NHANES data, respectively. The participants were censored at the date of admission, death due to any causes, or by December 31, 2005.

2.3. Definition of the metabolic syndrome

In this study, we used the recently harmonised definition jointly proposed by the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity [19]. This joint statement for the metabolic syndrome suggested the use of national or regional cut-offs for waist circumference [19]. The Korean Society for the Study of Obesity (KSSO) proposed 90 cm and 85 cm for the appropriate abdominal obesity for Korean men and women, respectively [20]. Thus, the definition of the metabolic syndrome in this study requires at least three of the following five components: (a) central obesity (waist circumference: $\geq$90 cm for Korean men, $\geq$85 cm for Korean women), (b) hypertriglyceridemia ($\geq$150 mg/dl), (c) low HDL cholesterol (men < 40 mg/dl, women < 50 mg/dl), (d) high blood pressure (systolic blood pressure $\geq$130 mmHg, diastolic blood pressure $\geq$ 85 mmHg or receiving hypertension drug treatment), and (e) hyperglycemia (fasting serum glucose $\geq$ 100 mg/dl). Participants receiving diabetes drug treatments or having fasting serum glucose of $\geq$126 mg/dl were excluded since our study examined the relationship of baseline metabolic syndrome with future diabetes events.

2.4. Variables on bio-clinical factors, health behaviours, family medical history, and socio-demographic factors

Details regarding bio-clinical factors (height, body weight, waist circumference, blood pressure, serum triglyceride, HDL cholesterol, and fasting glucose levels), health behaviours (cigarette smoking, alcohol consumption, and physical exercise), family history (hypertension/stroke, ischaemic heart disease, and diabetes), and socio-demographic factors (education, income, and marital status) are provided in Supplementary Data.

2.5. Statistical analysis

We calculated the prevalence of metabolic syndrome components according to the new harmonised definition. Cox proportional hazard models were used to estimate relative risk (RR) and their 95% confidence intervals (CIs) of cardiovascular disease, stroke, ischaemic heart disease, and diabetes associated with the metabolic syndrome after adjusting for covariates. Three models were created to assess the relationship of the metabolic syndrome with outcomes: model I adjusted for survey year (1998 and 2001) and age (age and age squared); model II adjusted for cigarette smoking, LDL cholesterol, alcohol consumption, and physical exercise as well as the covariates in model I; model III adjusted for socioeconomic status (education and household income), marital status, family history, and resting heart rate as well as the covariates in model II. For the analyses combining men and women, gender was additionally adjusted for in the model. We also assessed RRs according to the number of metabolic syndrome components and the individual component of the metabolic syndrome using Cox's regression. The population attributable risk fraction (PAR) was also estimated with IRAP (Interactive Risk Attributable Program) version 2.2 [21]. Except for PAR, other analyses were performed with SAS statistical software (SAS Institute Inc., Cary, NC).

3. Results

The study cohort contained 56,722 person–years (for cardiovascular disease) of follow-up (average length of follow-up = 5.8 years). We found 288 cases of cardiovascular disease events during the follow-up period (see Supplementary Fig. 1). The numbers of morbidity or mortality events for stroke, ischaemic heart disease, and diabetes were 184, 122, and 85, respectively. For 18 individuals, both stroke and ischaemic heart disease occurred. Of the total 71 cardiovascular and 4 diabetes deaths, 58 (81.7%) and 4 (100%) were hospitalised with the same diagnosis during the follow-up period.

Baseline characteristics of men and women aged 20+ who participated in the 1998 and 2001 Korea National Health and Nutrition Examination Surveys were presented in Supplementary Table 1. The prevalence of metabolic syndrome was 24.2% in men and

Table 1
Relative risk (RR) and population attributable risk fraction (PAR %) and their 95% confidence intervals (CI) of cardiovascular disease, stroke, ischaemic heart disease, and diabetes mellitus by metabolic syndrome after adjustment of covariates among 9791 men and women aged 20+: findings from follow-up data of the 1998 and 2001 Korea National Health and Nutrition Examination Surveys.

	All (n = 9791)		Men (n = 4391)		Women (n = 5400)	
	RR (95% CI)	PAR (95% CI)	RR (95% CI)	PAR (95% CI)	RR (95% CI)	PAR (95% CI)
Cardiovascular disease						
Model I	1.48 (1.17 – 1.89)†	14.0 (5.1 – 22.9)	1.51 (1.08 – 2.12)*	12.2 (1.4 – 22.9)	1.31 (0.93 – 1.84)	12.1 (−3.3 – 27.4)
Model II	1.43 (1.12 – 1.82)†	13.3 (4.5 – 22.4)	1.49 (1.06 – 2.10)*	12.1 (1.2 – 22.9)	1.29 (0.91 – 1.82)	10.8 (−5.2 – 26.7)
Model III	1.43 (1.12 – 1.82)†	13.1 (4.0 – 22.3)	1.53 (1.09 – 2.16)*	12.3 (1.5 – 23.1)	1.30 (0.92 – 1.84)	11.1 (−4.9 – 27.0)
Stroke						
Model I	1.39 (1.03 – 1.88)*	12.1 (0.7 – 23.4)	1.42 (0.92 – 2.21)	10.4 (− 3.5 – 24.3)	1.33 (0.88 – 2.00)	12.4 (−6.3 – 31.0)
Model II	1.36 (1.01 – 1.84)*	11.7 (0.1 – 23.3)	1.45 (0.93 – 2.25)	10.6 (− 3.4 – 24.6)	1.32 (0.87 – 2.01)	11.7 (−7.4 – 30.8)
Model III	1.35 (1.00 – 1.83)	11.6 (0.0 – 23.2)	1.49 (0.95 – 2.33)	10.9 (− 3.0 – 24.8)	1.30 (0.85 – 1.98)	11.7 (−7.6 – 30.9)
Ischaemic heart disease						
Model I	1.64 (1.13 – 2.36)†	17.2 (3.7 – 30.8)	1.77 (1.06 – 2.94)*	17.2 (0.6 – 33.7)	1.18 (0.70 – 2.00)	8.1 (−16.1 – 32.3)
Model II	1.54 (1.06 – 2.22)*	15.9 (1.7 – 30.1)	1.70 (1.02 – 2.83)*	16.7 (− 0.1 – 33.5)	1.13 (0.67 – 1.93)	5.4 (−20.9 – 31.6)
Model III	1.58 (1.09 – 2.29)*	15.8 (1.5 – 30.0)	1.75 (1.05 – 2.94)*	16.4 (− 0.4 – 33.2)	1.21 (0.71 – 2.08)	6.5 (−19.6 – 32.6)
Diabetes mellitus						
Model I	2.27 (1.47 – 3.51)‡	27.6 (12.1 – 43.0)	2.43 (1.40 – 4.22)†	27.6 (8.6 – 46.6)	1.92 (0.94 – 3.92)	25.6 (−1.6 – 52.7)
Model II	2.16 (1.39 – 3.36)‡	26.6 (10.5 – 42.6)	2.41 (1.38 – 4.22)†	27.5 (8.1 – 46.9)	1.75 (0.84 – 3.64)	23.0 (−5.8 – 51.8)
Model III	2.12 (1.36 – 3.30)‡	25.6 (9.3 – 41.9)	2.51 (1.43 – 4.40)†	27.1 (7.5 – 46.7)	1.94 (0.91 – 4.14)	23.3 (−5.4 – 52.0)

Note. Model I: survey year and age (age and age square) were adjusted. Model II: besides the variables in model I, cigarette smoking, LDL cholesterol, alcohol consumption, and physical exercise were additionally adjusted. Model III: besides the variables in model II, socioeconomic status (education and household income), marital status, family histories (hypertension/stroke, ischaemic heart disease/heart failure, and diabetes), and resting heart rate were additionally adjusted.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$.

21.8% in women. Prevalences (%) of components of the metabolic syndrome according to the new harmonised definition were also presented in Supplementary Table 2.

The metabolic syndrome was significantly associated with increased risks of all four outcomes in the base model (model I) when men and women were combined (Table 1). The magnitude of the relationship tended to be greater for diabetes than cardiovascular diseases. Those with the metabolic syndrome had 2.27 times (95% CI: 1.47–3.51) greater risk of diabetes but 1.48 times (95% CI: 1.17–1.89) greater risk of cardiovascular disease. These significant associations were more evident in men than women, especially for ischaemic heart disease. The magnitude of relationships between the metabolic syndrome and outcomes did not change significantly after adjustment of covariates including health behaviours, socioeconomic status, marital status, family history, and other biological factors (LDL cholesterol and resting heart rate). Table 1 also presents the PARs and associated 95% CIs showing that about a quarter of total diabetes occurrence and more than 10% of cardiovascular disease was attributable to the metabolic syndrome. When we included diabetes patients (those receiving diabetes drug treatment and those with fasting serum glucose of 126 mg/dl or over) at baseline in our analyses given that diabetes can be seen as a metabolic risk factor, magnitudes of the relationships between the metabolic syndrome and outcomes were similar for cardiovascular disease, stroke, and ischaemic heart disease, but tended to become greater for diabetes (see Supplementary Table 3).

Fig. 1 presents the RRs (95% CI) of four outcomes by the number of metabolic syndrome components. Considering the small number of outcomes in gender-specific analysis, we only present the results combining men and women. The RRs increased as the number of metabolic syndrome components increased (all P for trend < 0.01). The increasing patterns were especially remarkable for diabetes. Those with five components of the metabolic syndrome had an 8 times (HR 8.13, 95% CI: 2.43–27.15) greater risk of future diabetes events.

Table 2 shows the RRs (95% CI) of future health events when all five components of the metabolic syndrome were simultaneously adjusted in the survey year- and age-adjusted model. High blood pressure was significantly associated with all four health outcomes when men and women were combined (Table 2). Significantly increased risks of hypertriglyceridemia were found for cardiovascular disease and ischaemic heart disease. Hyperglycemia was significantly associated with future diabetes events. The association of high blood pressure with stroke was greater in women than in men (P for interaction = 0.043) while the association of hypertriglyceridemia with stroke tended to be greater in men than in women (P for interaction = 0.066). The gender difference in the relationship between high blood pressure and cardiovascular disease was also significant (P for interaction = 0.019) mainly because of the gender difference in the relationship of high blood pressure with stroke. No other significant gender differences were found. Models adjusted for only an individual component produced greater RRs than those reported in Table 2 (see Supplementary Table 4), but the analysis results did not affect the above conclusion. Table 2 also presents the PARs (95% CI) after simultaneous adjustment of metabolic syndrome components, showing high blood pressure contributes substantially to the occurrence of cardiovascular disease and diabetes. A total of 32.7% (95% CI: 20.1–45.2%) and 26.8% (95% CI: 4.2–49.4%) of cardiovascular disease and diabetes occurrence, respectively, were attributable to high blood pressure. Hyperglycemia explained 33.6% (95% CI: 16.5–50.8%) of diabetes events and 24.5% (95% CI: 10.8–38.2%) of ischaemic heart disease was attributable to hypertriglyceridemia.

4. Discussion

This study provides evidence that the metabolic syndrome is associated with increased risk of cardiovascular diseases and diabetes in Korea. Men and women with the metabolic syndrome had 48%, 39%, 64%, and 127% greater risks of cardiovascular disease, stroke, ischaemic heart disease, and diabetes, respectively, than those without the metabolic syndrome. The increased risks of cardiovascular disease, ischaemic heart disease, and diabetes remained significant after adjusting for a wide range of covariates including major health behaviours (cigarette smoking, alcohol consumption, and physical exercise), bio-clinical factors (LDL cholesterol and resting heart rate), related family history (hypertension/stroke, ischaemic heart disease/heart failure, and

Table 2
Simultaneously adjusted relative risk (RR), population attributable risk fraction (PAR %) and their 95% confidence intervals (CI) of cardiovascular disease, stroke, ischaemic heart disease, and diabetes by individual component of metabolic syndrome among 9791 men and women aged 20+: findings from follow-up data of the 1998 and 2001 Korea National Health and Nutrition Examination Surveys.

	Cardiovascular disease		Stroke		Ischaemic heart disease		Diabetes	
	RR (95% CI)	PAR (95% CI)	RR (95% CI)	PAR (95% CI)	RR (95% CI)	PAR (95% CI)	RR (95% CI)	PAR (95% CI)
All								
Central obesity	1.01 (0.78 – 1.31)	0.4 (−7.4 – 8.3)	1.02 (0.73 – 1.41)	0.6 (−9.4 – 10.6)	0.95 (0.63 – 1.42)	−1.5 (−13.4 – 10.5)	1.33 (0.84 – 2.11)	9.2 (−6.1 – 24.4)
Hypertriglyceridemia	1.40 (1.10 – 1.80)†	12.6 (3.3 – 21.9)	1.19 (0.87 – 1.62)	6.4 (−5.5 – 18.3)	1.97 (1.35 – 2.87)‡	24.5 (10.8 – 38.2)	1.34 (0.85 – 2.12)	11.6 (−6.1 – 29.2)
Low HDL cholesterol	1.02 (0.79 – 1.32)	1.1 (−10.5 – 12.7)	1.14 (0.83 – 1.57)	6.0 (−8.6 – 20.6)	0.83 (0.56 – 1.23)	−8.6 (−27.5 – 10.3)	1.22 (0.76 – 1.96)	8.0 (−11.2 – 27.2)
High blood pressure	1.86 (1.42 – 2.43)‡	32.7 (20.1 – 45.2)	2.01 (1.43 – 2.84)‡	36.9 (21.4 – 52.4)	1.63 (1.08 – 2.45)*	26.2 (6.0 – 46.5)	1.67 (1.03 – 2.69)*	26.8 (4.2 – 49.4)
Hyperglycemia	0.95 (0.75 – 1.21)	−2.0 (−11.5 – 7.4)	0.86 (0.63 – 1.16)	−6.2 (−17.9 – 5.6)	1.24 (0.86 – 1.77)	8.2 (−6.4 – 22.8)	2.29 (1.47 – 3.54)‡	33.6 (16.5 – 50.8)
Men								
Central obesity	1.19 (0.82 – 1.73)	4.4 (−5.5 – 14.3)	1.16 (0.71 – 1.88)	3.8 (−8.9 – 16.4)	1.33 (0.76 – 2.32)	7.6 (−8.1 – 23.3)	1.37 (0.75 – 2.50)	9.1 (−9.6 – 27.8)
Hypertriglyceridemia	1.59 (1.13 – 2.25)†	18.7 (5.2 – 32.3)	1.65 (1.06 – 2.57)*	20.0 (2.7 – 37.3)	1.63 (0.97 – 2.76)	20.2 (−0.9 – 41.3)	1.46 (0.81 – 2.61)	16.4 (−7.0 – 39.9)
Low HDL cholesterol	0.93 (0.64 – 1.36)	−2.1 (−13.3 – 9.0)	1.02 (0.63 – 1.65)	0.7 (−13.7 – 15.1)	0.86 (0.48 – 1.52)	−4.9 (−22.0 – 12.2)	1.40 (0.77 – 2.57)	10.1 (−7.4 – 27.5)
High blood pressure	1.41 (0.99 – 2.00)	18.5 (0.1 – 37.0)	1.37 (0.87 – 2.16)	17.7 (−7.2 – 42.5)	1.49 (0.87 – 2.55)	21.0 (−5.9 – 47.9)	1.52 (0.84 – 2.76)	22.1 (−7.6 – 51.8)
Hyperglycemia	0.92 (0.66 – 1.29)	−3.4 (−16.4 – 9.6)	0.83 (0.54 – 1.29)	−7.3 (−23.8 – 9.2)	1.04 (0.63 – 1.73)	1.4 (−19.0 – 21.9)	1.99 (1.14 – 3.48)*	28.3 (5.7 – 50.9)
Women								
Central obesity	0.86 (0.60 – 1.23)	−5.2 (−17.4 – 7.0)	0.92 (0.59 – 1.41)	−3.0 (−18.2 – 12.2)	0.65 (0.36 – 1.17)	−14.7 (−32.1 – 2.8)	1.26 (0.61 – 2.57)	8.4 (−16.4 – 33.1)
Hypertriglyceridemia	1.17 (0.82 – 1.68)	5.4 (−7.1 – 18.0)	0.86 (0.55 – 1.35)	−5.2 (−20.7 – 10.4)	2.09 (1.21 – 3.62)†	24.9 (6.5 – 43.2)	1.17 (0.55 – 2.49)	5.1 (−21.2 – 31.3)
Low HDL cholesterol	1.10 (0.77 – 1.57)	5.9 (−15.4 – 27.1)	1.27 (0.82 – 1.96)	13.7 (−11.3 – 38.7)	0.77 (0.45 – 1.34)	−16.0 (−52.7 – 20.6)	1.01 (0.49 – 2.08)	1.5 (−45.0 – 48.1)
High blood pressure	2.46 (1.60 – 3.78)‡	45.9 (28.7 – 63.1)	3.14 (1.82 – 5.42)‡	54.6 (35.5 – 73.7)	1.49 (0.80 – 2.80)	24.2 (−8.6 – 56.9)	2.02 (0.86 – 4.71)	35.6 (0.8 – 70.3)
Hyperglycemia	0.93 (0.66 – 1.30)	−3.1 (−17.3 – 11.1)	0.83 (0.55 – 1.27)	−7.4 (−24.7 – 9.8)	1.34 (0.80 – 2.25)	12.6 (−9.4 – 34.6)	2.70 (1.32 – 5.53)†	40.7 (14.0 – 67.4)

Note. Central obesity (waist circumference for men ≥ 90 cm, for women ≥ 85 cm), hypertriglyceridemia (serum triglyceride ≥ 150 mg/dl), low HDL cholesterol (serum HDL cholesterol for men < 40 mg/dl, for women < 50 mg/dl), high blood pressure (systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or receiving hypertension drug treatments), hyperglycemia (fasting blood glucose ≥ 100 mg/dl). All five components of the metabolic syndrome were simultaneously adjusted to estimate relative risk and population attributable risk fraction for in the survey year- and age-adjusted model.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$.

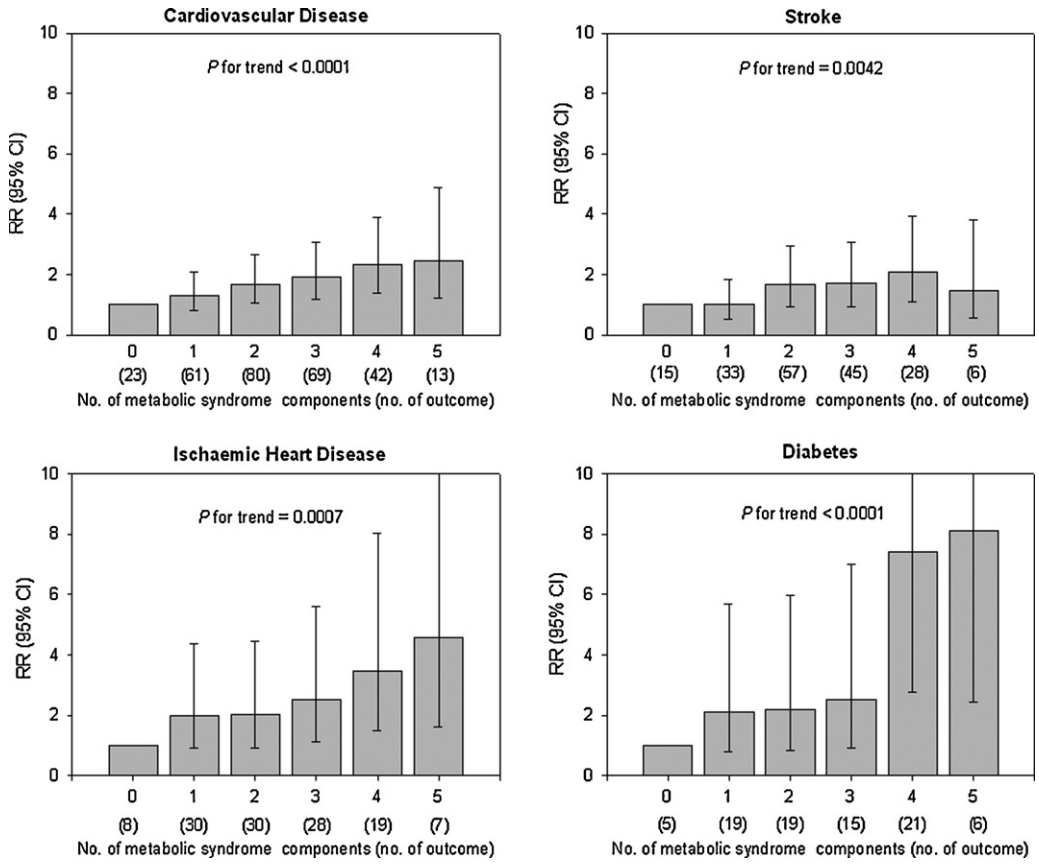

Fig. 1. Numbers of metabolic syndrome components and associated outcomes and relative risks (HR) (95% confidence intervals, CI) of cardiovascular disease, stroke, ischaemic heart disease, and diabetes among 9791 men and women aged 20+: findings from follow-up data of the 1998 and 2001 Korea National Health and Nutrition Examination Surveys.

diabetes) and socio-demographic factors (education, income, and marital status).

The magnitude of association between the metabolic syndrome and health outcomes may vary with study design (e.g., definition of the metabolic syndrome, duration of follow-up, level of follow-up loss, and covariates adjusted), study subjects (e.g., race, gender, prevalence of the metabolic syndrome, and pre-morbid conditions), and health outcomes [2–7]. This study showed that the magnitude of the RR and PAR differed by gender and health outcome. The gender differences in the RR and PAR were more evident for ischaemic heart disease than stroke and diabetes. The PARs for stroke and diabetes were relatively similar in men and women (see Table 1). Prior meta-analyses have shown greater RR of cardiovascular disease and stroke in women than men [3,4,6,7]. The Hisayama study showed that the RR of ischaemic heart disease was greater in men than in women but vice versa for stroke [10]. However, in a Hong Kong study, the metabolic syndrome was significantly associated with vascular mortality in men, not in women [9]. Meanwhile, results of our study showed that the RR for incident diabetes was greater than the RR for cardiovascular disease. This finding is congruent with previous studies that the metabolic syndrome in many populations predicts incident diabetes more strongly than it predicts cardiovascular disease [2,5].

The analysis according to the number of metabolic syndrome components showed that there was no apparent threshold relationship between the metabolic syndrome and health outcomes (see Fig. 1). Several Asian studies have shown linear relationships between metabolic risk factors and cardiovascular disease (stroke and ischaemic heart disease) [9,10,12–15,22]. The RR increase by the number of components was especially significant for diabetes. The RR of incident diabetes for those with five abnormal components of the metabolic syndrome was 8.13 (95% CI: 2.43–27.15). However, the risks of diabetes according to the number of abnormal metabolic risk factors have rarely been reported in Asia [22].

This study showed that high blood pressure was an important determinant of cardiovascular disease and diabetes. After simultaneous adjustment of five metabolic syndrome components, high blood pressure was significantly associated with increased risks of cardiovascular disease, stroke, ischaemic heart disease, and diabetes. According to the PARs, high blood pressure also explained a substantial proportion of the occurrence of cardiovascular disease (about a third) and diabetes (about a fourth). Many Asian studies revealed a more important role for high blood pressure than other components in determining future cardiovascular events [12–14]. Prior Chinese and Japanese studies have shown that elevated blood pressure was the only significant predictor of cardiovascular events [12,13]. Our study also indicated that hypertriglyceridemia and hyperglycemia explained a fourth of ischaemic heart disease and a third of diabetes, respectively. According to a recent meta-analysis, the strongest predictor of diabetes was the impaired fasting glucose [5]. It should be noted that, in our study, the significant RR of incident diabetes-associated hyperglycemia came from the study sample without baseline diabetes after excluding known diabetes patients and subjects with fasting blood glucose of $\geq$126 mg/dl at the baseline survey.

This study presented the statistically significant gender difference in the relationship between high blood pressure and stroke. The magnitude of the relationship was greater in women than in men. In a prior Japanese study, the relationship of systolic and diastolic blood pressure with stroke among ages 65–79 was greater

in women than in men [23]. It has been suggested that gender difference in arterial structure and function may lead to gender difference in the relationship of risk factors with stroke [24]. Considering the potential gender difference in the profiles of risk factors in predicting stroke incidence [25], more studies on the gender difference would be helpful in better understanding stroke and other cardiovascular diseases.

This study has limitations. First, outcome ascertainment was not done by active surveillance of the study subjects during the follow-up periods, but based on the electronic data linkage to secondary data (death certificate and hospitalisation data). Although the completeness of these secondary data can reach 100%, the accuracy of diagnosis of a disease may be suboptimal. According to our analysis, 81.7% of total cardiovascular deaths (58 of 71) and 4 (100%) of 4 diabetes had been admitted to hospitals because of the same disease. Prior Korean studies showed that diagnostic accuracy of hospitalisation data was 83.0% for stroke and 85.6% for ischaemic heart disease [26,27]. Some diabetes patients might have only sought primary health care during the follow-up period without using any hospital inpatient care. However, information on the diagnostic accuracy of diabetes in hospitalisation data as well as the proportion of diabetes patients only seeking primary health services without hospital cares during the 6 years was not available. These less optimal levels of outcome ascertainment, especially for diabetes, might have resulted in reduced (rather than enhanced) magnitude of the RR and PAR between the metabolic syndrome and health outcome because baseline metabolic syndrome status may not be related to accuracy of diagnosis in hospitalisation data and death certificate data. Nevertheless, analysis results showed that the relationship between metabolic syndrome and diabetes was stronger than those for ischaemic heart disease and stroke. Second, the duration of follow-up was relatively short and the number of deaths was relatively small. This hindered further subgroup analyses (e.g., analysis by age groups and stroke subtype) and may have resulted in wide 95% CIs for RRs and PARs. However, there are mixed findings on the magnitude of association by duration of follow-up [4,7].

This study also has strengths. First, we used the longitudinal follow-up data of a nationally representative sample with information about waist circumference. Although the response rates of the K-NHANES were not 100% and some of samples (i.e., those with invalid personal identification numbers or missing data, pregnant women, those with stroke, ischaemic heart disease, diabetes, or cancer at baseline) were excluded, our study subjects include Korean men and women with various socio-demographic characteristics all over the country. Three prior longitudinal studies employed a nationally representative sample [12,17,18], but two studies from Japan and the US substituted body mass index as a measure for obesity [12,17] and a Turkish study examined the longitudinal relationship in a relatively short follow-up period (3-year follow-up) [18]. Second, we presented analysis results on stroke, ischaemic heart disease, and diabetes. To our knowledge, no Asian studies have presented results on cardiovascular events and diabetes simultaneously.

In summary, the metabolic syndrome was significantly associated with cardiovascular disease, ischaemic heart disease, and diabetes after adjustment of a wide range of covariates in a national longitudinal study. The RR and PAR for ischaemic heart disease were greater in men than women. The RR and PAR were greater for diabetes than stroke and ischaemic heart disease. The number of metabolic syndrome components was linearly associated with risks of all four health outcomes. Of the abnormal metabolic risk factors, high blood pressure was significantly associated with all four outcomes examined in this study while hypertriglyceridemia and hyperglycemia were also important for ischaemic heart disease and diabetes, respectively. Our findings suggest that reduction of metabolic risk factors is necessary in Korea to lower the burden of associated diseases, especially ever-increasing ischaemic heart disease and diabetes [28].

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2010.09.009.

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