Components of metabolic syndrome and their relation to the risk of incident cerebral infarction

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Abstract. Metabolic syndrome (MetS) consists of 5 metabolic components, which are recognized as risk factors for cerebral infarction. The present study was to evaluate the relative influence of individual metabolic component on incident cerebral infarction. Using a data of 209,339 Koreans registered in National Health Information Corporation, we evaluated the risk for incident cerebral infarction according to the number of metabolic component and each metabolic component for 4.37 years’ follow-up. Cox proportional hazards model was used to calculate hazard ratios (HRs) for cerebral infarction and their confidence interval (CI). The more metabolic components accompanied the worse metabolic profile, leading increased incidence of cerebral infarction. The risk of cerebral infarction increased proportionally to the number of present metabolic components (number 0: reference, number 1: 1.78 [1.42–2.23], number 2: 2.20 [1.76–2.74], number 3: 2.61 [2.09–3.25] and number 4–5: 3.18 [2.54–3.98]). Compared to subjects without metabolic component, the impact of each component on cerebral infarction was relatively higher in elevated fasting glucose (1.56 [1.14–2.13]) and elevated BP (2.13 [1.66–2.73]), indicating no statistical significance in low HDL-cholesterol (1.53 [0.96–2.44]), high triglyceride (1.24 [0.84–1.84]) and abdominal obesity (1.05 [0.63–1.73]). Proportional relationship was found between the number of metabolic component and risk of cerebral infarction. Out of metabolic components, fasting glucose and BP are more powerful predictor for cerebral infarction.

Key words: Metabolic syndrome, Impaired fasting glucose, Elevated blood pressure, Cerebral infarction

METABOLIC SYNDROME (MetS) represents a clustering of metabolic abnormalities that consists of abdominal obesity, impaired fasting glucose (FG), elevated blood pressure (BP) and dyslipidemia in triglyceride and high density lipoprotein (HDL) cholesterol [1]. It is established that the presence of MetS increases the risk of cardiovascular disease (CVD).

Cerebral infarction is a major complication of CVD with a synonym of ischemic stroke, accounting for third largest cause of death and the largest cause of adult disability in the U.S [2]. Previous studies have shown the significant association between ischemic stroke and MetS, in which the presence of MetS is a major risk factor of ischemic stroke [3-7]. MetS was associated with the increased risk for silent ischemic stroke as well as symptomatic lesion [8-10]. As a potential mechanism for the association, it has been documented that each metabolic component links to insulin resistance, adiposity, oxidative stroke, chronic inflammation and atherosclerosis, potentially resulting in ischemic stroke [11-13]. However, it is still under scrutiny in the degree to which specific metabolic component contributes to the risk of
cerebral infarction.

National Health Insurance Corporation (NHIC) is the Korea national institution that provides national health insurance service (NHIS) to Korean population. The data of NHIS was used in establishing National Health Insurance Service–National Sample Cohort (NHIS-NSC) in 2002 [14].

Using data of 209,339 Koreans from NHIS-NSC, we evaluated the risk of cerebral infarction according to the number of metabolic components. To identify the relative impact of each metabolic component on cerebral infarction, we compared the predictive ability of each metabolic component on cerebral infarction.

### Study Participants and Methods

#### Data sources

NHIS provides medical service to Koreans registered in NHIS, and covers about 97% of Korean population. The information derived from usage of NHIS is stored in the database of NHIS. The National Health Insurance Service–National Sample Cohort (NHIS-NSC) is a population-based cohort based on the database of NHIS. NHIS-NSC was first constructed in 2002, and randomly sampled 2.2% of 46,605,433 Korean populations who were registered in database of NHIS in 2002 [14]. Thus, total number of NHIS-NSC was 1,025,340 Koreans (2.2% of 46,605,433), and they were followed-up from 2002 to 2013. Out of data of NHIS-NSC, we were provided with data of 223,551 Koreans who received health check-up in 2009. Korean adults aged more than 40 years can receive medical health check-up at least once every two years, and their results of health check-up were stored in database of NHIS.

The study protocol was designed in compliance with the principles embodied in the Declaration of Helsinki (2013). Ethics approvals for the study protocol and analysis of the data were obtained from the institutional review board of Kyung Hee University Hospital.

#### Study participants

A total 223,551 subjects who received medical health check-up in 2009 were initial number of study participants. Among them, we excluded 2,387 subjects who were previously diagnosed as cerebral infarction (ICD: I63) between 2002 and 2009. Additionally, we further excluded 11,825 subjects who were relevant to following exclusion criteria: 217 subjects did not have the information about the components of MetS; 11,617 subjects were previously diagnosed as cancer (ICD: C00-C97) between 2002 and 2009. Because some subjects had more than one exclusion criteria, 209,339 subjects were included in the final analysis and were observed for the development of cerebral infarction. The total follow-up period was 914,775.6 person year and average follow-up period was 4.37 (standard deviation, 0.48) person year.

#### Health survey examinations and laboratory measurements

The baseline study data were derived from the examination of health check-up performed at 2009. The examination of health check-up includes a self-administered questionnaire, anthropometric measurements and laboratory measurements. Self-administered questionnaire presents smoking amount by pack-year, alcohol intake and physical activity. Anthropometric measurements consist of body weight (Kg), height (cm), body mass index (BMI), waist circumference (WC) and BP. The following laboratory data were measured at health check-up: fasting blood glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum creatinine (SCr), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT). Estimated glomerular filtration rate was used in assessing kidney function [15].

The presence of MetS was determined based on the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention [1]. MetS was defined as the presence of three or more components out of 5 metabolic components described as follows. Elevated BP was defined as a systolic and diastolic BP ≥130/85 mmHg; elevated fasting blood glucose level was defined as ≥100 mg/dL; high triglyceride levels were defined as ≥150 mg/dL; low HDL-cholesterol levels were defined as <40 mg/dL in men and <50 mg/dL in women; elevated WC was defined as ≥90 cm in men and ≥85 cm in women. Subjects with baseline hypertension, diabetes mellitus (DM) and dyslipidemia were regarded as subjects with a baseline metabolic component of elevated BP, elevated fasting glucose and high triglyceride, respectively. The identification of present baseline hypertension, DM and dyslipidemia was based on reviewing data for ICD code of hypertension (I10–I15), DM (E10–E14) and dyslipidemia (E78.0–E78.5) from 2002 to 2009 years (date of receiving medical health check-up in 2009).

#### Outcome definitions

The National Health Insurance database was linked to the diagnosis of diseases data from Statistics Korea. In this study, the entry date was the first health check-up time since 2009 and the last follow-up date for diagnosis of cerebral infarction was December 31, 2013. The diagnosis of cerebral infarction was defined as ICD I63. The primary clinical endpoint of interest for our study was
development of cerebral infarction a composite endpoint.

**Statistical analysis**

Data were expressed as means ± (standard deviation) or medians (interquartile range) for continuous variables and percentages of the number for categorical variables. The independent t-test and X²-test were used to analyze the statistical differences between baseline non-MetS and MetS. The one-way ANOVA and X²-test were used to analyze the statistical differences among characteristics of the study subjects at the time of enrollment in relation to the number of metabolic component. The number of metabolic component comprised the following: 0, 1, 2, 3 and 4–5. 4 (n = 22,241, 10.62%) and 5 (n = 5,697, 2.72%) was combined into 4–5 category for analyses, owing to the small number of 5. The person years were calculated as the sum of follow-up times from the baseline until the diagnosis time of cerebral infarction development or until the December 31, 2013.

To evaluate the associations of baseline number of metabolic component and incident cerebral infarction, we used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for incident cerebral infarction (adjusted HRs [95% CI]).

Cox-proportional hazard models were adjusted for the multiple confounding factors. In the multivariate models, we included variables that might confound the relationship between MetS and cerebral infarction, which include: age, gender, eGFR, GGT, smoking amount (pack-year), alcohol intake and physical activity. To test the validity of the Cox-proportional hazard models, we checked the proportional hazard assumption. The proportional hazard assumption was assessed by log-minus-log survival function and found to be graphically unviolated. p values <0.05 were considered to be statistically significant. All statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA).

**Results**

During 914,775.6 person-years of follow-up, 2,402 (1.15%) cases of cerebral infarction developed between 2009 and 2013. The baseline characteristics of the study subjects in relation to MetS are presented in Table 1. At baseline, the mean (SD) age and BMI of study subjects were 57.8 (8.6) years and 24.0 (2.9) kg/m², respectively. There were significant differences in all of the listed variables between non-MetS group and MetS group except for SCr.

Supplementary Table 1 shows the baseline characteristics of study subjects according to the number of MetS components. There were clear dose response relationships between all of the listed variables and the number of metabolic component.

In contrast to subjects without incident cerebral infarction, those with incident cerebral infarction were older (66.7 vs. 57.7) and more likely to have a less favorable metabolic profiles at baseline (Supplementary Table 2).

Table 2 shows the hazard ratios and 95% confidence interval for cerebral infarction according to the number of metabolic component. In multivariate adjusted model, the adjusted HRs and 95% CI for cerebral infarction increased proportionally to the number of metabolic components (number 0: reference, number 1: 1.78 [1.42–2.23], number 2: 2.20 [1.76–2.74], number 3: 2.61 [2.09–3.25] and number 4: 3.18 [2.54–3.98]).

The relative risk of individual metabolic component on incident cerebral infarction was presented in Table 3. Compared to subjects without any present metabolic component, subjects with each elevated fasting glucose (1.56 [1.14–2.13]) and elevated BP (2.13 [1.66–2.73]) had the significantly increased risk for cerebral infarction. However, other components didn’t show the significant association with the risk of cerebral infarction.

When 71,762 subjects with MetS were categorized by fasting glucose (normal <100 mg/dL, impaired fasting glucose: 100–125 mg/dL and DM >126 mg/dL), and BP (normal <120/80 mmHg, prehypertension: 120–139/80–89 mmHg and hypertension ≥140/90 mmHg), Each DM and hypertension was more significantly associated with increased risk of cerebral infarction than normal fasting glucose and normal BP, respectively (Table 4).

**Discussion**

In the present study, the risk of cerebral infarction increased proportionally to the number of present metabolic component. Compared with subjects without metabolic component, subjects with three metabolic components fulfilling diagnostic criteria of MetS had more than two-fold risk for cerebral infarction (2.61 [2.09–3.25]), and subjects with four or more metabolic components presented more than three-fold risk for cerebral infarction (3.18 [2.54–3.98]).

Previous studies also showed the proportional relationship between the number of metabolic component and the risk of CVD. In a 5 years’ follow-up for 4,423 individuals, the risk for CVD including ischemic stroke increased proportionally to the number of present metabolic component compared with no metabolic component (odds ratio: 1.95 [0.91–4.16] in one component, 2.05 [0.96–4.40] in two components, 2.70 [1.22–5.98] in three components and 5.86 [2.51–13.66] in four components) [16]. Koren-Morag et al. showed that odds ratio of ischemic stroke increased at the presence of more than
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Table 1 Baseline characteristics of study participants according to the presence of MetS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Non-MetS (N = 137,577)</th>
<th>MetS (N = 71,762)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-year (total)</td>
<td>914,775.6</td>
<td>601,313.6</td>
<td>313,462.0</td>
<td></td>
</tr>
<tr>
<td>Person-year (average)</td>
<td>4.37 ± (0.48)</td>
<td>4.37 ± (0.45)</td>
<td>4.36 ± (0.53)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.8 ± (8.6)</td>
<td>56.7 ± (8.2)</td>
<td>60.0 ± (9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>118,306 (56.5)</td>
<td>80,777 (58.7)</td>
<td>37,529 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>91,033 (43.5)</td>
<td>56,800 (41.3)</td>
<td>34,233 (47.7)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± (2.9)</td>
<td>23.2 ± (2.6)</td>
<td>25.6 ± (2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>82.1 ± (8.1)</td>
<td>79.6 ± (7.3)</td>
<td>86.8 ± (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>125.2 ± (15.2)</td>
<td>122.1 ± (14.4)</td>
<td>131.3 ± (14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77.7 ± (9.9)</td>
<td>76.1 ± (9.6)</td>
<td>80.7 ± (9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>200.4 ± (37.4)</td>
<td>199.7 ± (35.7)</td>
<td>203.7 ± (40.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>118 (83–171)</td>
<td>101 (74–135)</td>
<td>170 (121–230)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>55.4 ± (32.2)</td>
<td>58.4 ± (32.9)</td>
<td>49.7 ± (30.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>118.5 ± (39.0)</td>
<td>119.3 ± (37.6)</td>
<td>117.2 ± (41.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>100.7 ± (25.2)</td>
<td>95.4 ± (19.6)</td>
<td>111.0 ± (31.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>1.15 ± (1.49)</td>
<td>1.15 ± (1.49)</td>
<td>1.15 ± (1.49)</td>
<td>0.446</td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m²)</td>
<td>80.8 ± (20.2)</td>
<td>82.0 ± (20.0)</td>
<td>78.6 ± (20.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>24 (20–29)</td>
<td>23 (20–28)</td>
<td>25 (20–31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>21 (16–29)</td>
<td>20 (15–27)</td>
<td>24 (18–34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>25 (17–41)</td>
<td>23 (16–37)</td>
<td>30 (19–51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking amount (pack-year)</td>
<td>7.8 ± (13.8)</td>
<td>7.7 ± (13.5)</td>
<td>8.0 ± (14.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Alcohol intake (%)</td>
<td>14.7</td>
<td>14.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td>16.8</td>
<td>17.2</td>
<td>16.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incidence of cerebral infarction</td>
<td>2,402 (1.15)</td>
<td>1,172 (0.85)</td>
<td>1,230 (1.71)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are means (standard deviation), medians (interquartile range), or percentages.
* p-value by t-test for continuous variables and Chi squared test for categorical variables.

three metabolic components in 14,284 Israeli (odds ratio: 1.26 [0.72–2.20] in one component, 1.70 [0.98–2.95] in two components, 2.37 [1.36–4.16] in three components and 3.23 [1.82–5.74] in 4 to 5 components) [17]. However, their studies presented significant association only in three or more present metabolic components, and one or two present metabolic components didn’t show the significant association. In contrast, our results clearly identified the increased risk of cerebral infarction even at the presence of only one metabolic component. These findings suggest that early management for metabolic components is clinically important even before overt diagnosis of MetS in terms of preventing cerebral infarction.

When we investigated the relative risk of each component for incident cerebral infarction, elevated BP and elevated fasting glucose are associated with the increased risk of cerebral infarction. These findings are in line with previous results reporting that fasting glucose and BP are stronger arbiter for CVD than other metabolic components [6,18]. In particular, BP and fasting glucose was positively correlated with silent brain infarction, periventricular hyperintensity, and subcortical white matter lesions [9]. Despite some equivocal findings, it can be recognized that increase in BP and fasting glucose more strongly contributes to CVD than other metabolic components.

The pathological contribution of metabolic components to cerebral infarction may be characterized by insulin resistance and elevated BP. Fasting glucose ≥100 mg/dL directly reflects insulin resistance, encompassing impaired fasting glucose and overt diabetes. Insulin resistance promotes atherosclerotic processes including vascular endothelial dysfunction [19, 20], which can increase the risk of cerebral infarction through the pathogenesis of intracranial atherosclerosis [21]. High BP is...
the leading modifiable risk factor for both ischemic and hemorrhagic stroke [22]. Adrenergic activation is associated with insulin resistance and hypertension. Adrenergic stimulation promotes glycogenolysis in liver and inhibits glucose utilization in adipose tissue and skeletal muscle [23]. Sympathetic activation induces elevation in BP, heart rate and systemic resistance [24]. Therefore, it is inferred that adrenergic effect on cardiometabolic system may be an underlying mechanism for our findings.

Nonetheless, it should be highlighted that diverse risk factors can be involved in the pathophysiology of cerebral infarction. Postprandial hyperglycemia is a stronger risk factor for CVD than fasting hyperglycemia [25]. Even when fasting glucose and HbA1c are within normal ranges, postprandial hyperglycemia causes macrovascular complications including stroke [26]. Additionally, LDL is the most critical risk factors for CVD including cerebral infarction. Meta-analysis showed that each 1 mmol/L
reduction in LDL cholesterol was associated with 20% relative risk reduction in ischemic stroke [27]. Further studies should investigate underlying mechanisms for the association between metabolic components and cerebral infarction.

Two limitations exist in our study. First, relatively short follow-up period (4.73 years) limit the clear conclusion about the long-term influence of each metabolic component on cerebral infarction. Further studies should be conducted with longer follow-up period.

Second, the identification of cerebral infarction was based only on ICD code registered in database of NHIS. Although cerebral infarction is a synonym of ischemic stroke, there may be pathologic diversity according to location and condition of lesion. However, because we didn’t match with radiological findings, we couldn’t provide the interpretation based on the diversity of cerebral infarction.

In conclusion, the risk of cerebral infarction increased proportionally to the number of metabolic components. Out of metabolic components, elevated fasting glucose and BP were most powerful predictors for cerebral infarction. These results suggest that the risk of cerebral infarction varies within same category of MetS according to present metabolic components.

Conflict of Interest

None of the authors have any potential conflicts of interest associated with this research.

Funding Statement

No funding.

Table 4  Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of cerebral infarction according to the level of fasting glucose and blood pressure in subjects with metabolic syndrome

<table>
<thead>
<tr>
<th>Fasting glucose</th>
<th>Person-year</th>
<th>Incidence cases</th>
<th>Incidence density</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg/dL</td>
<td>112,198.8</td>
<td>396</td>
<td>35.3</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>100–125 mg/dL</td>
<td>148,490.7</td>
<td>530</td>
<td>35.7</td>
<td>1.02 (0.89–1.16)</td>
</tr>
<tr>
<td>≥126 mg/dL</td>
<td>52,772.6</td>
<td>304</td>
<td>57.6</td>
<td>1.64 (1.41–1.91)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Person-year</th>
<th>Incidence cases</th>
<th>Incidence density</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>20,494.6</td>
<td>41</td>
<td>20.0</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>77,793.1</td>
<td>190</td>
<td>24.4</td>
<td>1.22 (0.87–1.71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>215,174.4</td>
<td>999</td>
<td>46.4</td>
<td>2.32 (1.70–3.17)</td>
</tr>
</tbody>
</table>

Multivariate adjusted model was adjusted for age, gender, eGFR, GGT, smoking amount (pack-year), alcohol intake and physical activity. Normal blood pressure <120/80 mmHg, pre-hypertension: 120–139/80–89 mmHg and hypertension >140/90 mmHg

Data Statement

We used the National Health Insurance Service–National Sample Cohort database and the dataset was obtained from the National Health Insurance Service. It can be analyzed only by accessing the web, and sharing of the data is not permitted by the National Health Insurance Service.

Acknowledgements

We used the National Health Insurance Service–National Sample Cohort database and the dataset was obtained from the National Health Insurance Service. Our study findings were not related to the National Health Insurance Service.

Author Contribution

Jae-Hong Ryoo is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Sung Keun Park wrote a manuscript as a first author. Eunhee Ha, Min-Ho Kim, Chang-Mo Oh, Ju Young Jung, Yei Kim and Joong-Myung Choi made substantial contributions to the acquisition of the data and critical revision of the study protocol and manuscript.

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The authors have nothing to disclose IRB information: The present study was approved by Kyung Hee university hospital (Reference number: 2018-12-020).
References


